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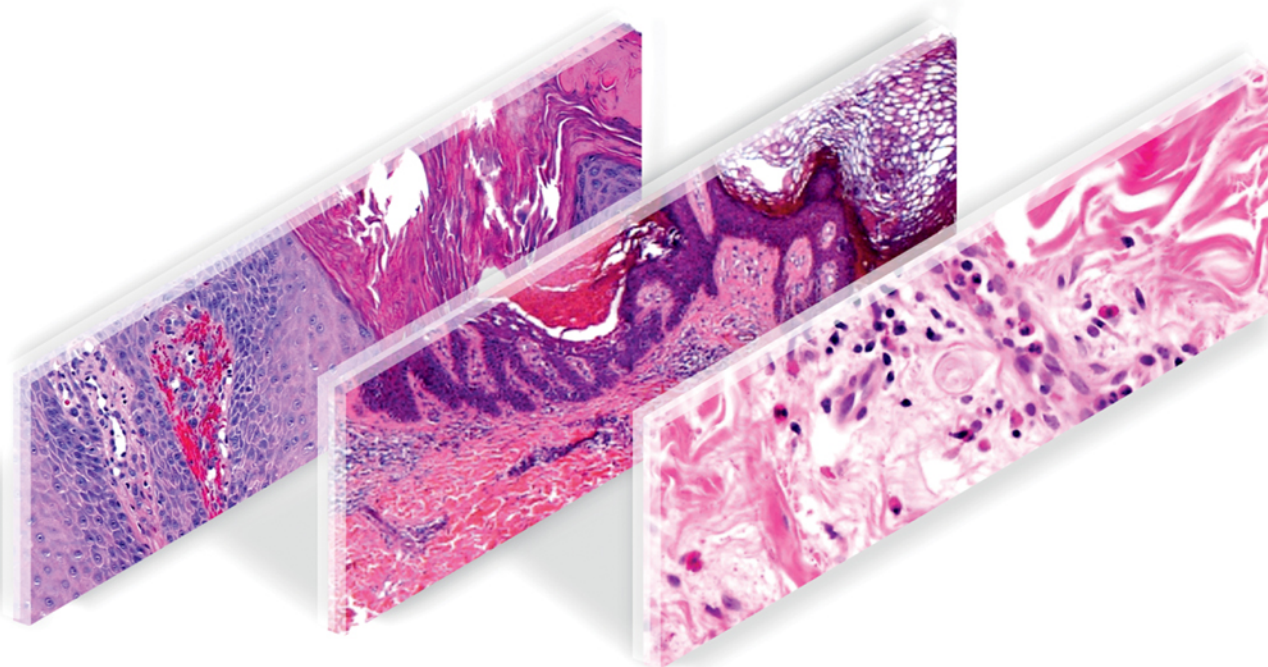
DIAGNOSTIC PATHOLOGY

# Nonneoplastic Dermatopathology

SECOND EDITION

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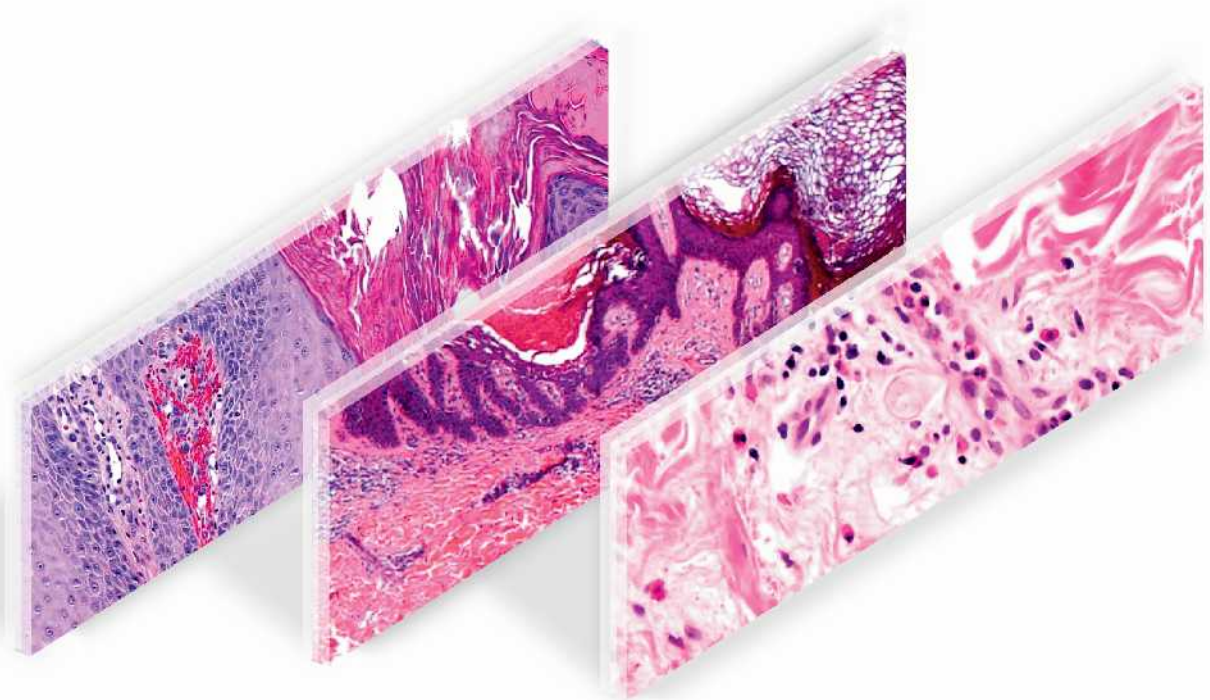
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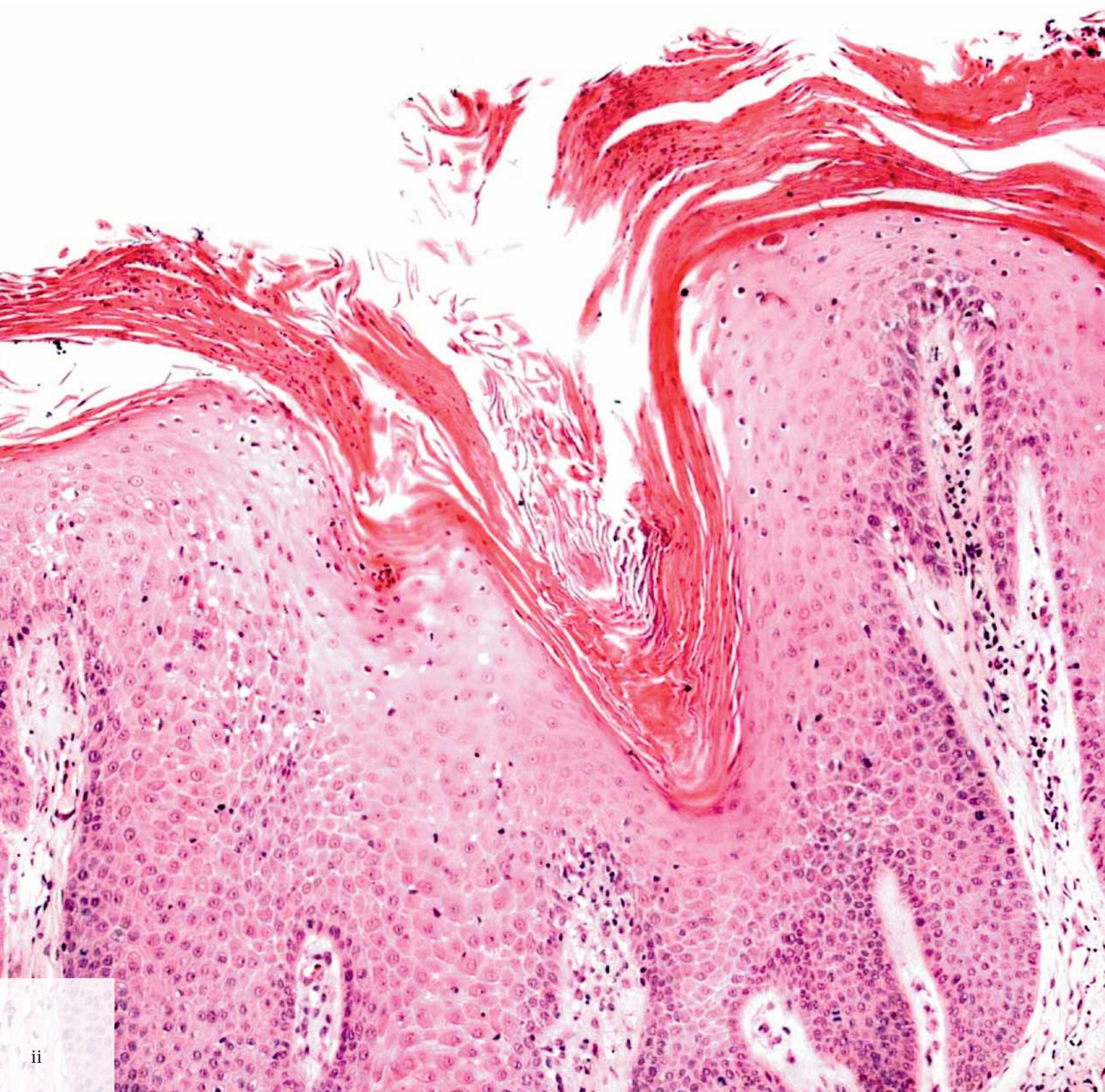
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**DIAGNOSTIC PATHOLOGY**

# Nonneoplastic Dermatopathology

**SECOND EDITION**

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# Dedications

*To my wife, Jamie, our Great Dane, Sadie, and all the wonderful, bright, hard-working, and dedicated authors who I have gotten to know over the years and have the pleasure of considering my close friends. I also want to thank all the contributors as well as authors for their selfless giving of images for chapters that were not their own. This book would not be possible without everyone listed in the table of contents as well as on the contributors page.*

**BJH**

*To my wife, Brenda, and children, Charlie and Lily, who have supported me so much in my life and in my career.*

**CJC**

*To my wife and kids, thank you for your unwavering love and support. For all the other contributors, thank you for your hard work and dedication to produce such a high-quality dermatopathology text. To me, Brian, and Travis: Strong work you rugged, chiseled gentlemen.*

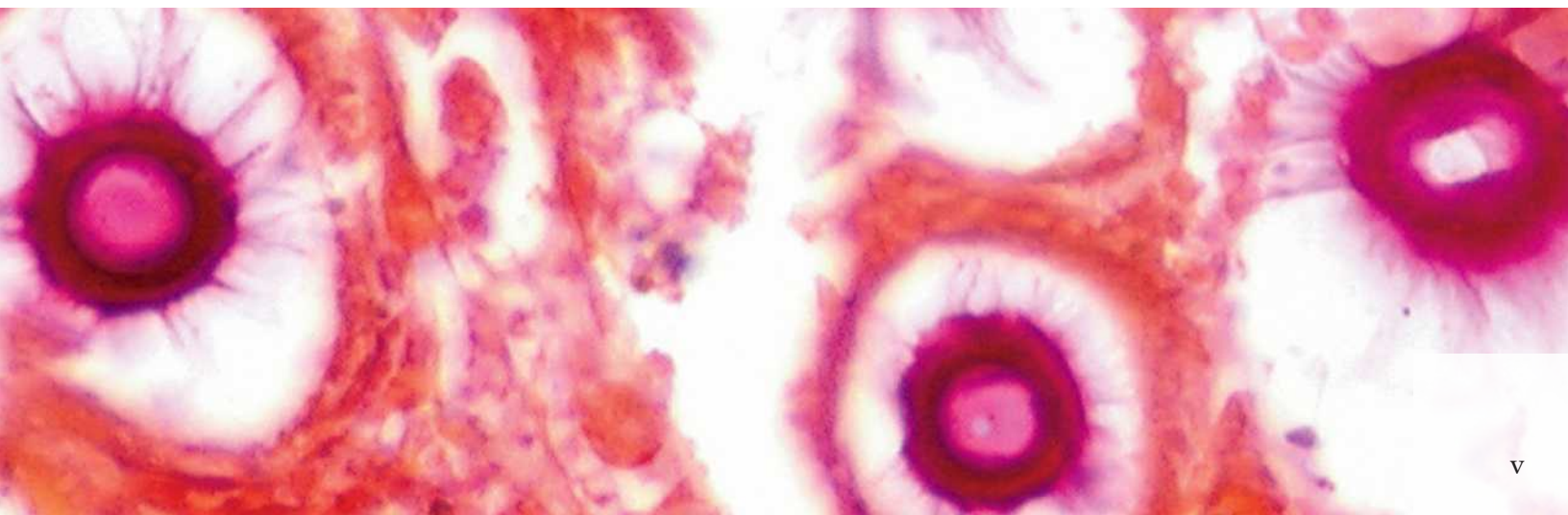
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*I would like to thank my incredibly loving and supportive wife, Clarissa, whose sacrifices have allowed me to work on this book. Equally as important, I would like to dedicate this endeavor to her, my sons, Carter and Clark, as well as the memory of my late parents, Don and Joyce.*

**CJ**

*To my mentors and colleagues, who teach me, and to my patients, who inspire me to keep learning.*

**TV**



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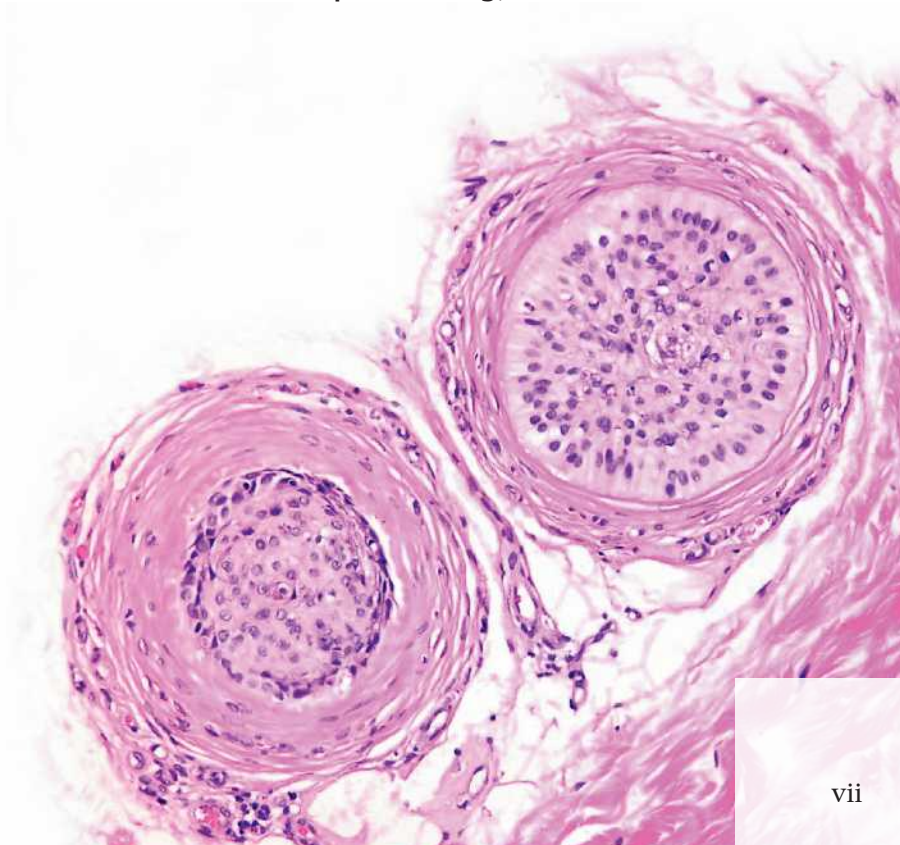
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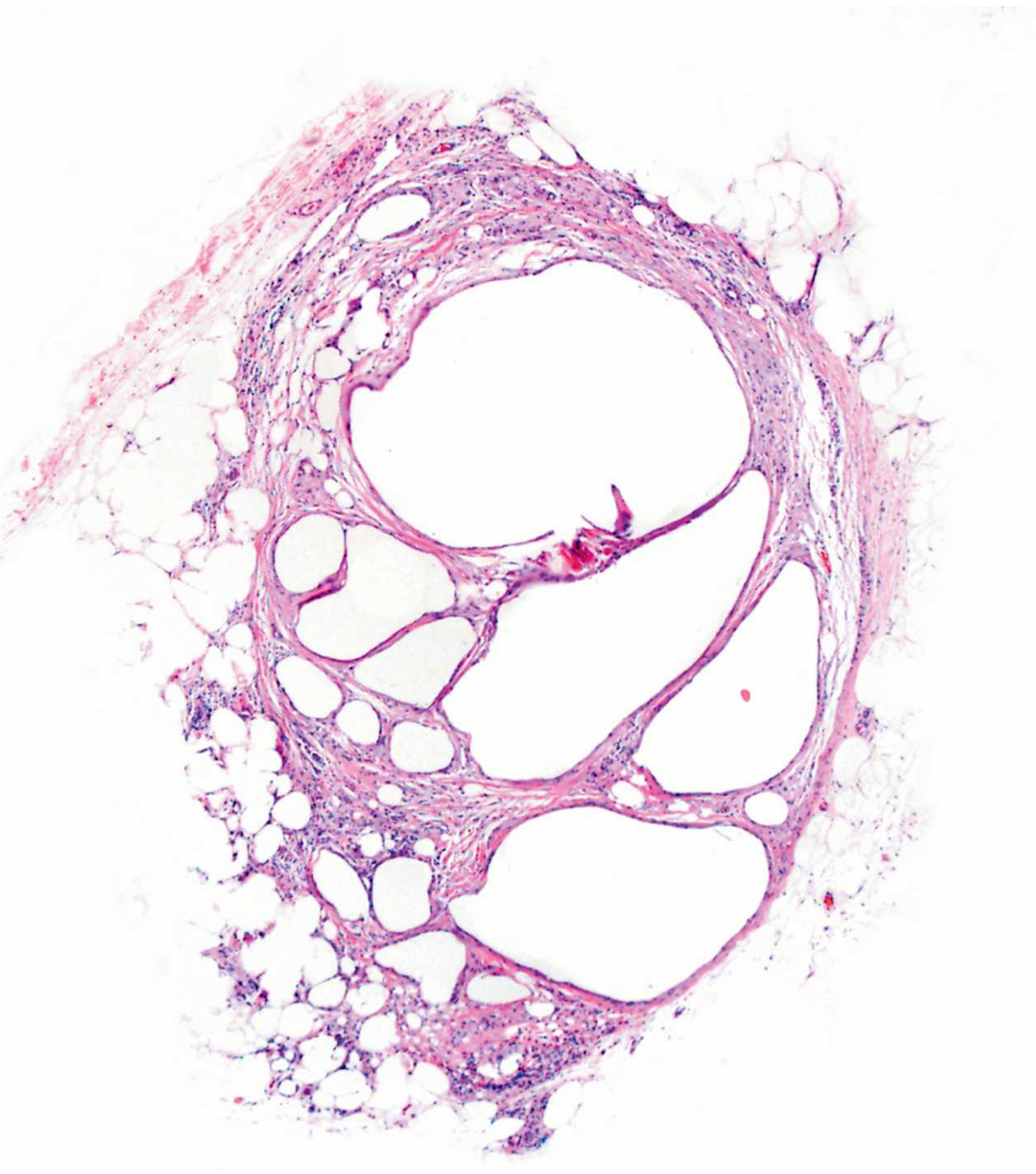
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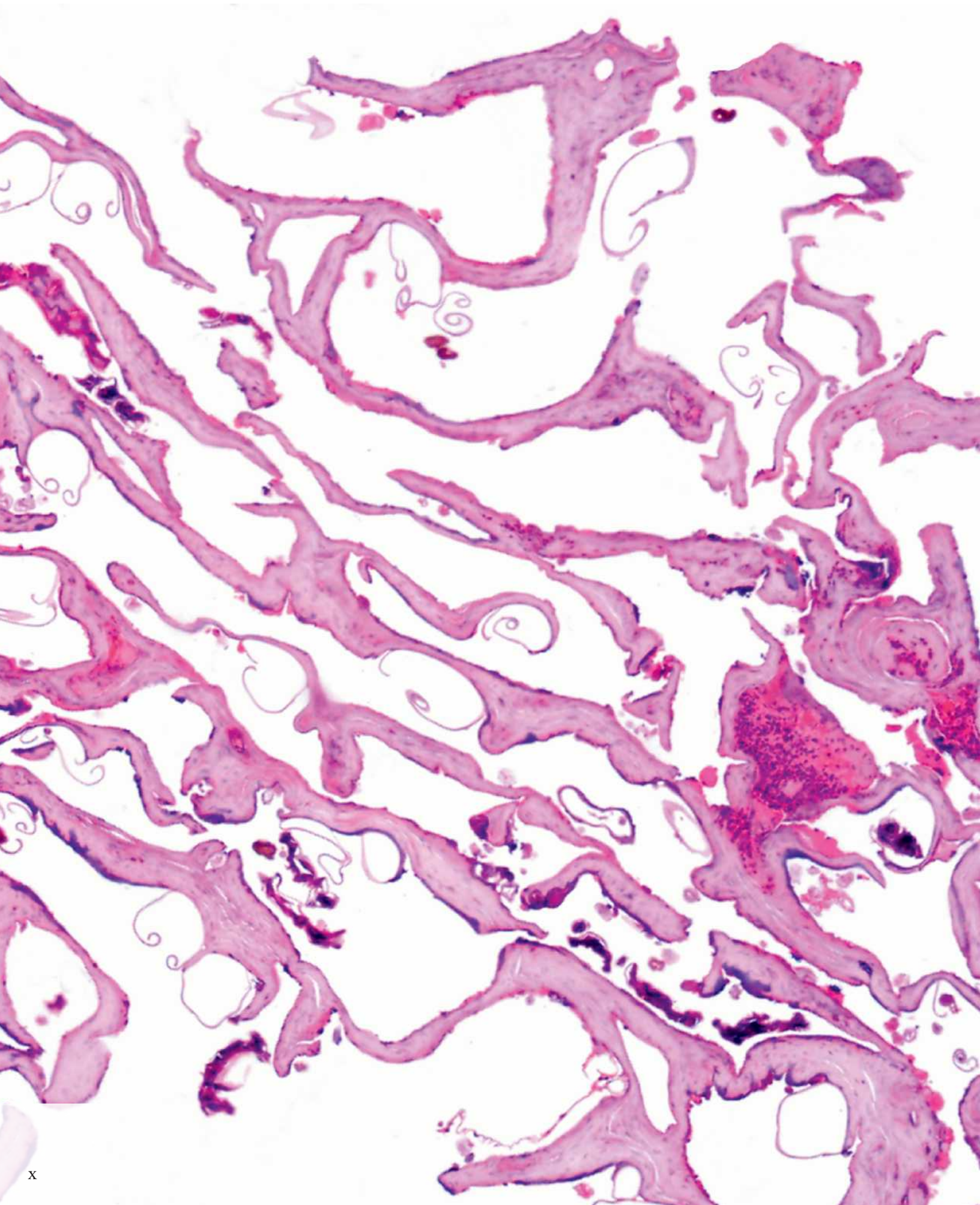




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# Preface

Nonneoplastic dermatopathology is sometimes seen as one of the most difficult parts of pathology residency training, and it can represent a very confusing subject for the general pathologist who does not see these types of cases on a regular basis. Part of the difficulty is due to the importance of clinical correlation. Although important in all of medicine, clinicopathologic correlation may be most important in nonneoplastic dermatopathology, as clinically striking lesions can have near normal histologic findings, and prominent histologic changes may lead to less than impressive clinical manifestations. Moreover, many clinical entities are not often seen or taught outside of a specific rotation in dermatology or dermatopathology.

*Diagnostic Pathology: Nonneoplastic Dermatopathology*, Second Edition therefore includes clinical images of nearly all the entities discussed, 250 in all (with approximately 90 new entities in this second edition). We hope that in-training and practicing pathologists will gain a better understanding of the clinical and histopathologic appearance of these lesions and, more importantly, their major histologic and clinical differential diagnoses.

We also anticipate that dermatologists and dermatopathologists can benefit from this book. Classic histologic images highlight the most important findings, allowing more confident diagnoses and histologic differential diagnoses. This book can also be used as a great study aid for fellows studying for their dermatopathology boards. The quality of the more than 1,500 clinical and histologic images in this book is not easily matched, thanks to the many contributing authors and the work of the image editors at Elsevier.

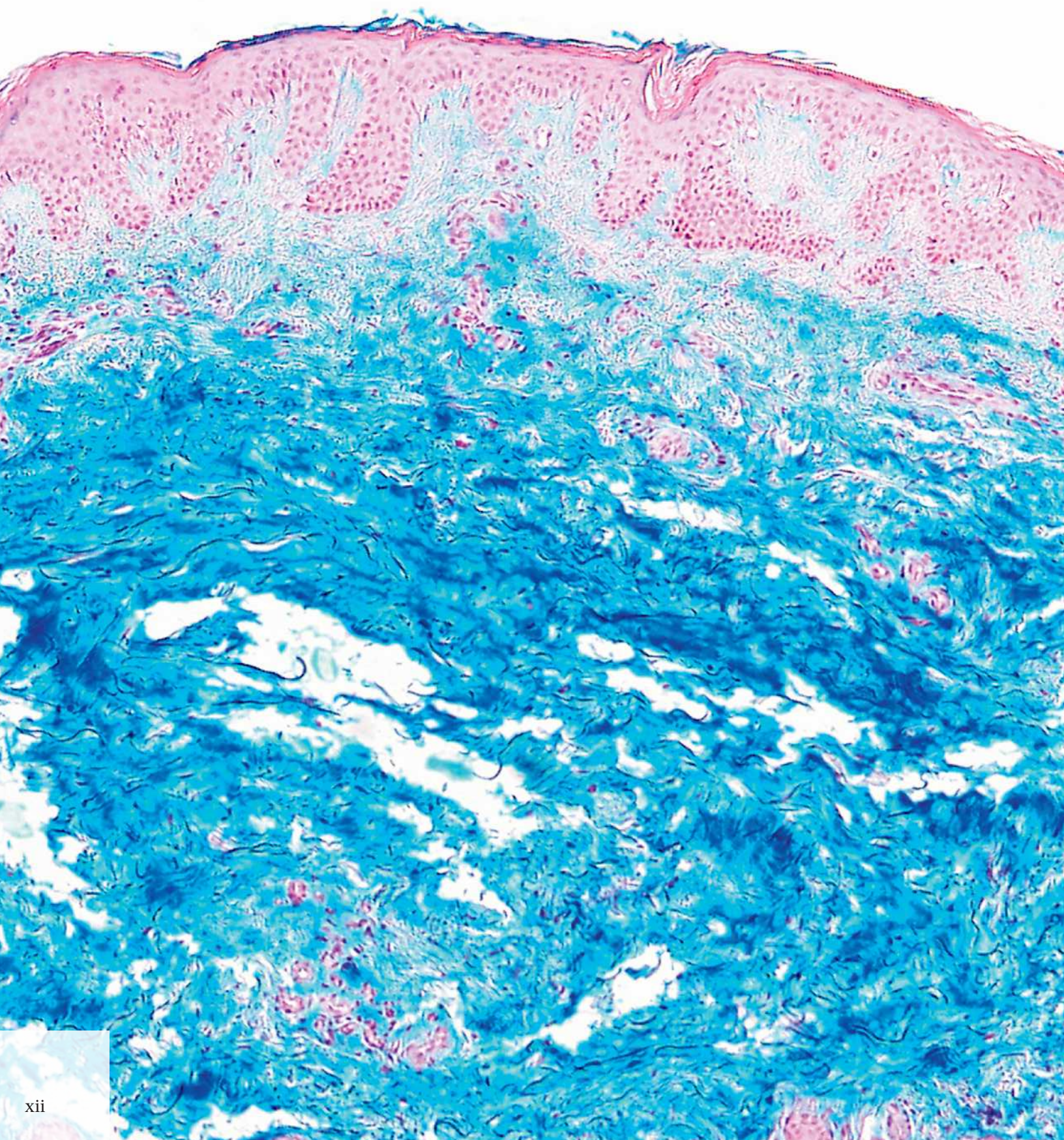
The book is organized into major histologic reaction patterns &/or disease categories. Within each section, we have attempted to organize entities in order of decreasing frequency usually encountered in general practice. We have also added numerous entities in this second edition in the hopes of producing a more consummate tome.

Our hope is to make the confusing subject of inflammatory dermatopathology much easier to comprehend and master, such that no important diagnoses will be easily overlooked or missed, therefore, improving patient care whether offered by pathologists or dermatologists. The eBook version of this book, Expert Consult, makes *Diagnostic Pathology: Nonneoplastic Dermatopathology* a comprehensive and easily searchable reference.

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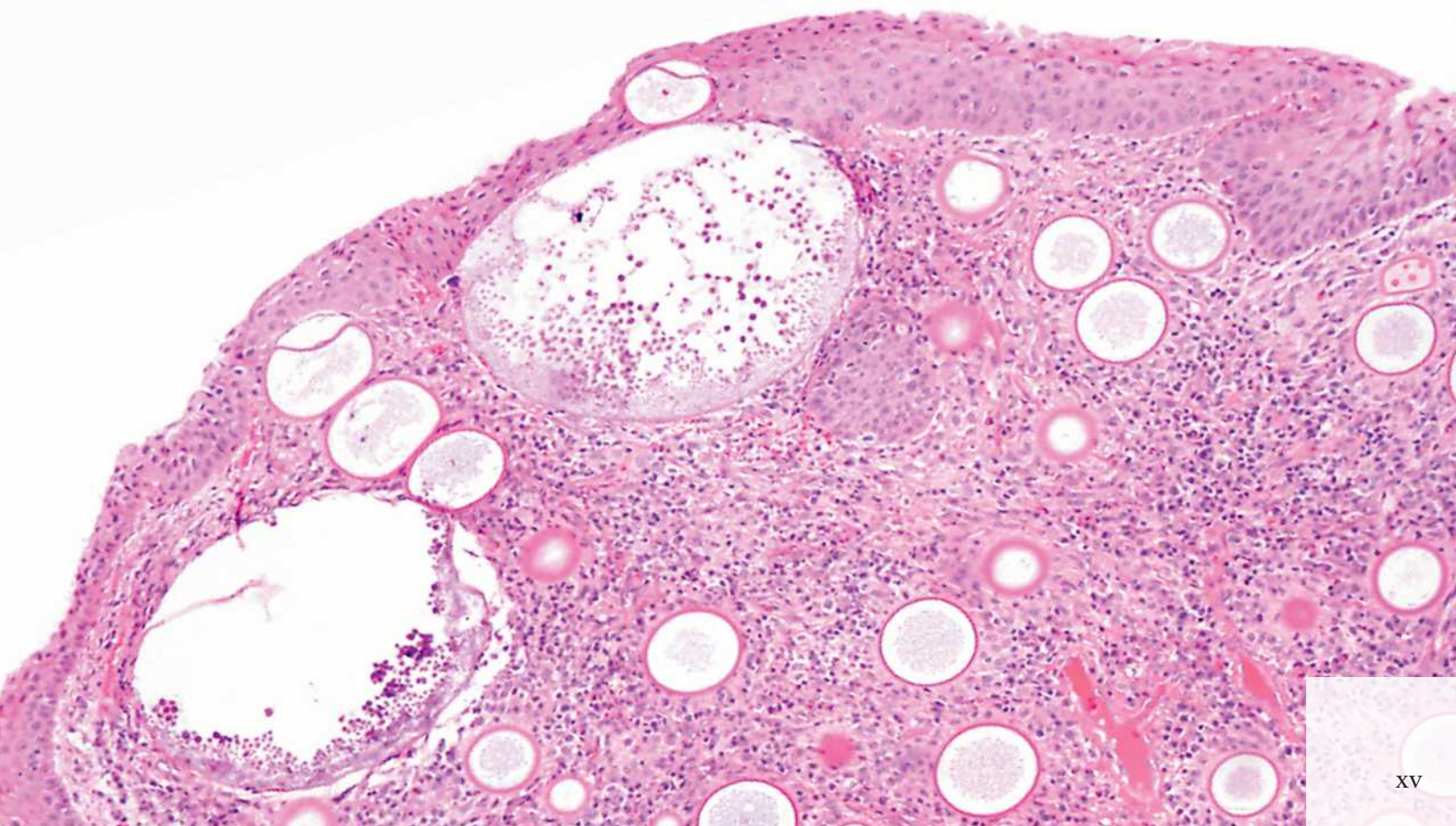
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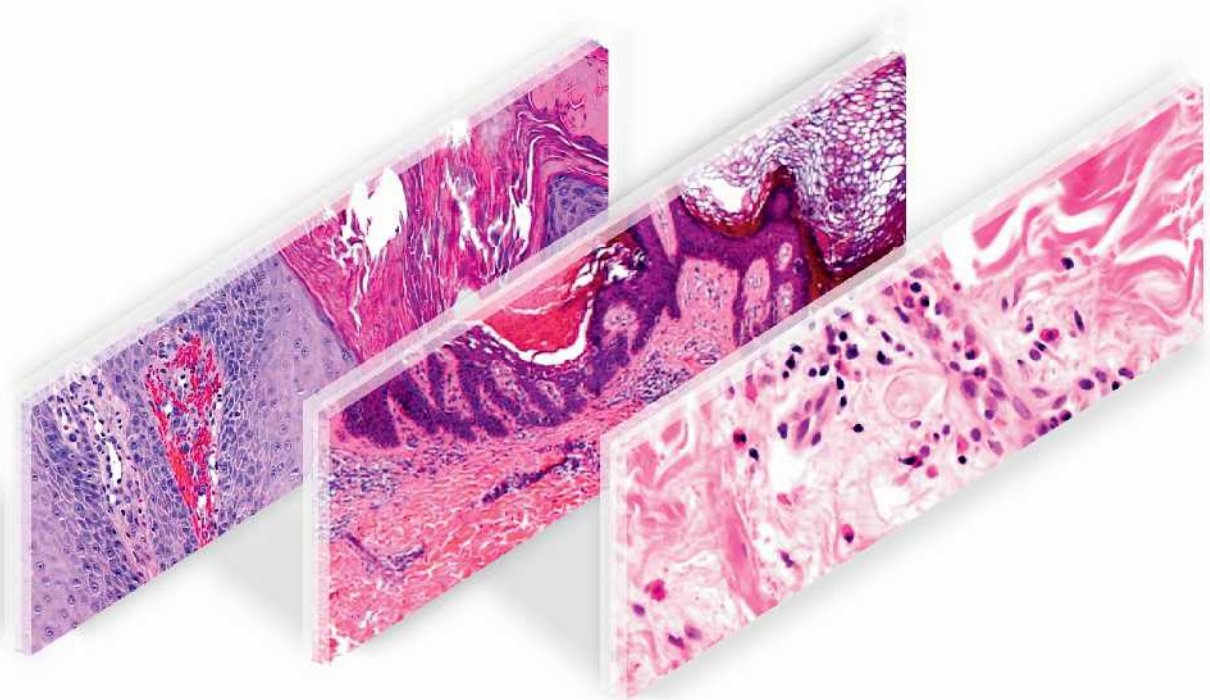
DIAGNOSTIC PATHOLOGY

# Nonneoplastic Dermatopathology

SECOND EDITION

**HALL | COCKERELL**

CHISHOLM • JESSUP • VANDERGRIFF • MOTAPARTHI • ELSTON

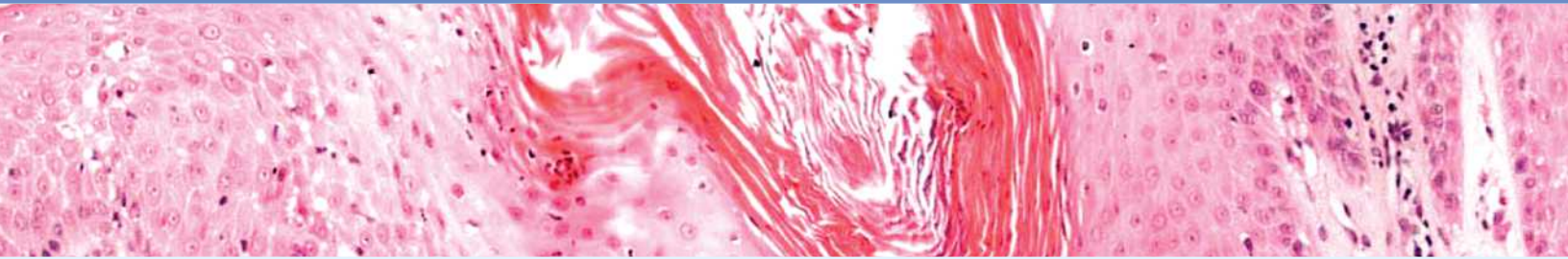


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## KEY FACTS

### TERMINOLOGY

- Chronic dermatitis with itching

### ETIOLOGY/PATHOGENESIS

- Activated T cells (Th2)
- 73% with positive family history of atopy
- Mutations in filaggrin seen in atopic dermatitis (AD)
- Staphylococcus aureus* in 90% of AD
- Predisposed to cutaneous viral and fungal infections

### CLINICAL ISSUES

- Acute: Vesicles with serous fluid, intense pruritus, papules and plaques with lichenification
- Subacute: Papules and plaques with excoriation
- Chronic: Thickened plaque with lichenification involving antecubital fossa, posterior neck, wrists, and ankles

### MICROSCOPIC

- Acute: Microvesicles with spongiosis and superficial perivascular lymphocytes
- Subacute: Spongiosis with parakeratosis and superficial dermal lymphocytes
- Chronic: Epidermal acanthosis with mild spongiosis

### TOP DIFFERENTIAL DIAGNOSES

- Scabies
- Psoriasis
- Other spongiotic dermatitides
- Dermatitis herpetiformis
- Cutaneous T-cell lymphoma

Acute Eczema Over Back

(Left) Acute eczema over the back of this patient is excoriated with oozing from open wounds. (Right) This chronic lesion shows mild spongiosis with irregular epidermal acanthosis. There is compact orthokeratosis and hypergranulosis, which are features of chronic rubbing.

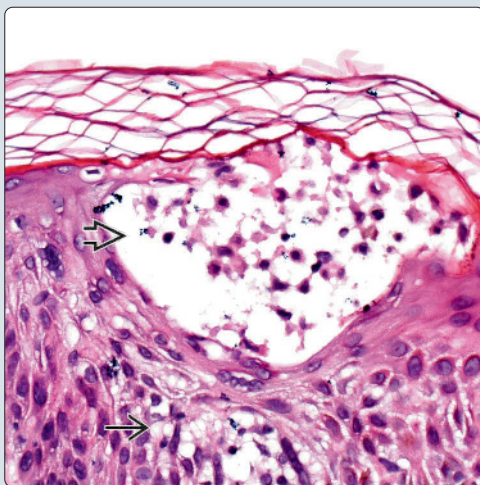


Spongiotic Dermatitis With Microvesicles

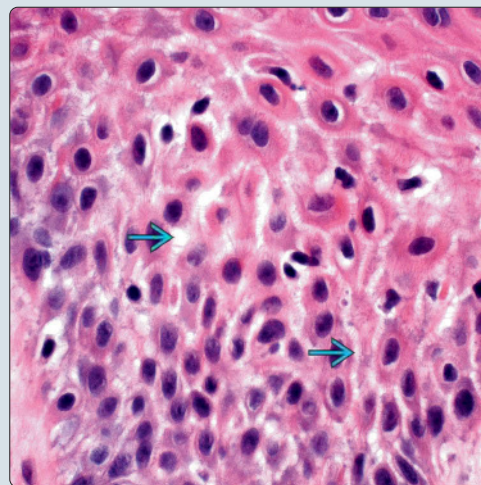


Spongiotic Microvesicle High Power

(Left) Acute lesion of atopic dermatitis (AD) shows a vesicle with abundant epidermal spongiosis (intercellular edema). (Right) High-power view of AD shows spongiosis of the epidermis (intercellular edema).



Intercellular Edema of Spongiosis



**TERMINOLOGY****Abbreviations**

- Atopic dermatitis (AD)

**Synonyms**

- Atopic eczema, eczema

**Definitions**

- Chronic dermatitis with itching and often history of atopy (asthma, allergic rhinitis, food allergies)

**ETIOLOGY/PATHOGENESIS****Infectious Agents**

- *Staphylococcus aureus* in 90% of AD

**Genetic Factors**

- 73% with positive family history of atopy

**Immunologic Factors**

- Activated T cells (Th2)

**CLINICAL ISSUES****Epidemiology**

- Age
  - 90% with onset before 5 years

**Presentation**

- Infancy
  - Initially involves creases with eventual spread to cheeks, scalp, and extensor surfaces
  - Ill-defined, erythematous patches and plaques; xerosis
  - Severe pruritus with uncontrollable scratching
- Childhood
  - Involved areas often have prominent lichenification
    - Most prominent in creases (antecubital fossa, popliteal fossa, gluteal-thigh creases)
  - Crusting and excoriation common
- Adults
  - Xerosis and erythema are more diffuse; lichenification may be present
  - Macular ring of hyperpigmentation may be seen around neck due to amyloid deposition

**Treatment**

- Drugs
  - Emollients, topical corticosteroids, topical calcineurin inhibitors, systemic steroids, antimicrobials, antihistamines
  - More systemic immune modulators in severe cases
- Others
  - Avoidance of triggers
  - Phototherapy

**Prognosis**

- Benign disease, but most children have disease persisting into adulthood

**MICROSCOPIC****Histologic Features**

- Findings similar to those seen in other spongiotic dermatitides
  - Acute: Microvesicles with spongiosis and superficial perivascular lymphocytes
  - Subacute: Spongiosis with parakeratosis and superficial dermal lymphocytes
  - Chronic: Epidermal acanthosis with mild spongiosis

**ANCILLARY TESTS****Serologic Testing**

- Serum IgE level determined by radioallergosorbent test (RAST)

**DIFFERENTIAL DIAGNOSIS****Histological**

- **Other spongiotic dermatitides**
  - Identical histologically in many instances
- **Dermatophytosis**
  - Need PAS or GMS to rule out tinea
- **Psoriasis**
  - Acanthosis, but should be minimal spongiosis
  - Loss or decreased granular layer
  - Neutrophils in spinous layer of epidermis (Kogoj pustules)
- **Cutaneous T-cell lymphoma**
  - More lymphocytes extending into epidermis
  - Less spongiosis and less parakeratosis
  - Lymphocytes lining up at dermoepidermal junction

**Clinical**

- **Other spongiotic dermatitides**
  - Clinical history may identify triggers of allergic or irritant contact dermatitis
  - Nummular patches in nummular dermatitis
  - Treatment is similar, and distinguishing between spongiotic dermatitides may not be reliable
- **Dermatophytosis**
  - Usually localized annular patch or plaque
- **Psoriasis**
  - Well-defined patches and plaques with silver scale
  - Positive Auspitz sign
  - Mediated by Th1 T cells
- **Cutaneous T-cell lymphoma**
  - Poikiloderma patches and plaques ± scale
  - Often annular, serpiginous, or geometric in shape
  - Pruritus not prominent feature

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# Contact Dermatitis

## KEY FACTS

### TERMINOLOGY

- Allergic contact dermatitis (ACD): Inflammatory skin disorder initiated by contact with allergen to which person has already been sensitized
- Irritant contact dermatitis (ICD): Inflammatory skin condition produced in response to nonimmune-mediated direct toxic effect of chemical or physical irritant substance damaging skin barrier

### CLINICAL ISSUES

- Prevalence of contact dermatitis (irritant and allergic) in USA varies from 1.5-5.4%
- In USA, *Rhus* dermatitis due to poison ivy/oak/sumac causes more cases of ACD than all other allergens combined
- ICD is most common job-related skin disease

### MICROSCOPIC

- Allergic and irritant contact dermatitis often not reliably distinguished due to overlap of histologic features

- Both have varying degrees of spongiosis depending on whether it is acute, subacute, or chronic
- May or may not have eosinophils in dermal infiltrate
- ICD often has degree of epidermal necrosis (single cell, patchy, or confluent)

### DIAGNOSTIC CHECKLIST

- ACD and ICD may appear histologically similar, which makes separation difficult
- Acute ACD shows prominent spongiosis with vesicles, neutrophils, superficial perivascular lymphohistiocytic dermal infiltrates with eosinophils and no epidermal necrosis
- Chronic ACD may show parakeratosis, minimal spongiosis, and epidermal hyperplasia and may even resemble lichen simplex chronicus
- ICD shows epidermal necrosis, ballooning, dyskeratotic keratinocytes, and less spongiosis, but features vary and may simulate ACD

**Irritant Contact Dermatitis to Glove**

**(Left)** Irritant contact dermatitis of the hand is a nonimmune-mediated injury resulting in well-demarcated erythematous, crusted plaques at points of contact with the inciting irritant glove material. **(Right)** Allergic contact dermatitis (ACD) with a well-demarcated erythematous plaque in an area of skin contact with offending allergen (an adhesive in this case) shows sparing where gauze prevented contact.



**Allergic Contact Dermatitis to Adhesive**

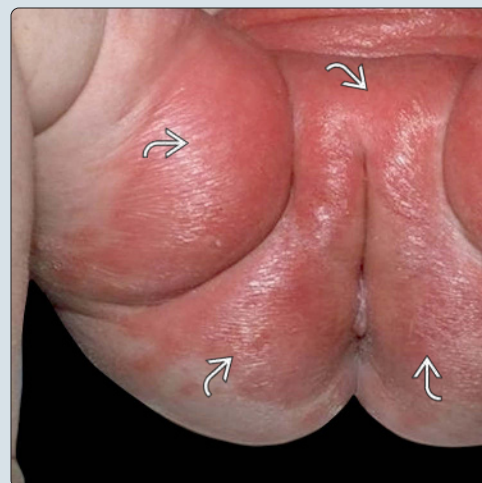


**Sandal Allergic Contact Dermatitis on Bilateral Feet**

**(Left)** The well-demarcated erythematous plaques of ACD seen on the dorsal feet bilaterally correspond to areas of the feet in direct contact with sandals that served as the offending antigen in this case. **(Right)** "Diaper rash," depicted here, is one of many expressions of irritant contact dermatitis. The rash results from prolonged direct exposure to feces and urine, leading to nonimmune-mediated injury.



**Diaper Rash**



## TERMINOLOGY

### Abbreviations

- Allergic contact dermatitis (ACD)
- Irritant contact dermatitis (ICD)

### Synonyms

- Hand dermatitis, diaper rash, and chemical dermatitis refer to types of ICD
- ACD may be referred to as eczematous dermatitis by some clinicians

### Definitions

- **ACD**
  - Inflammatory skin disorder initiated by contact with allergen to which person has already been sensitized
  - Caused by cutaneous type IV cell-mediated delayed hypersensitivity allergic reaction
- **ICD**
  - Inflammatory skin condition produced in response to nonimmune-mediated direct toxic effect of chemical or physical irritant substance damaging skin barrier
  - Irritants cause damage in many ways such as removal of surface lipids, damage of cell membranes, denaturation of epidermal keratins, cytokine release, and direct cytotoxic effect

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- **ACD**
  - Depends on sensitization, usually requires at least 2 exposures to exogenous antigen, and occurs only in sensitized individuals
  - Common allergens include nickel, fragrances, cosmetics, urushiol found in *Rhus* and *Toxicodendron* spp. (poison ivy/oak/sumac), formaldehyde, topical antibiotics, latex, rubber, balsam of Peru
- **ICD**
  - Acute form can occur upon even single exposure to toxic agent with severe cases resulting in necrosis
  - Commonly due to repeated or continuous exposures to alkaline soaps/detergents, organic solvents, and excess moisture (hand, diaper area, colostomy site)
  - Common irritants include acids, alkalis, cement, metal salts, phenols, kerosene, ethylene glycol, lime acids, plants, alcohol solvents, acetone, fiberglass

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Prevalence of contact dermatitis (ICD and ACD) in USA varies from 1.5-5.4%
- **ACD**
  - Affects limited number of sensitized people, yet it is common and accounts for up to 20% of all cases of dermatitis in children
  - Sensitization to nickel is leading cause of ACD worldwide
  - In USA, *Rhus* dermatitis due to poison ivy/oak/sumac causes more cases of ACD than all other allergens combined

- **ICD**
  - Increased susceptibility (thin stratum corneum) in 15% of people, but anyone can be affected
  - Most common job-related skin disease (80% of cases)

### Site

- **ACD**
  - Localized to 1 region or generalized in random pattern or on exposed areas
  - Initially confined to area of allergen contact and may be linear
- **ICD**
  - Acute forms may be localized or generalized depending on nature of contact with toxic agent; chronic form commonly affects hands

### Presentation

- **ACD**
  - Immune-mediated reaction that may spread to involve adjacent skin or even beyond affected site with rare generalized involvement
  - Rapid onset once sensitized usually 12-48 hours after antigen exposure and persisting up to 3-4 weeks
  - Can occur with as few as 2 exposures (poison ivy) or require many exposures with weaker allergens
  - Intense pruritus and even pain with fever and acute illness syndrome in severe cases
  - Appearance of skin lesions depends on severity and location and evolves over time
    - Acute: Well-demarcated erythematous plaques and edema with superimposed vesicles &/or papules with bullae and confluent erosions in severe cases
    - Subacute: Plaques of mild erythema with small, dry scales and small firm papules are seen
    - Chronic: Lichenified plaques; scaling with small, firm, round to flat papules; and excoriations with erythema and pigmentation
  - Special variants include systemic, airborne, urticarial, and allergic phytocontact dermatitis
- **ICD**
  - Toxic phenomenon confined to exposed area, so it is always sharply marginated and never spreads
  - Occurs minutes after exposure or may be delayed over 24 hours; hands most common site affected
  - Skin lesions range from sharply demarcated erythema with dry, cracked, fissured, crusted skin to vesicles and caustic burn with necrosis
  - Configuration of lesions is often linear or irregular suggesting "outside job" effect
  - Requires 1 to many exposures depending on traits of person's epidermal barrier with typically gradual onset as barrier becomes compromised
  - Special forms include hand dermatitis, airborne, pustular, and acneiform variants

### Laboratory Tests

- **ACD**
  - Positive skin patch tests
- **ICD**
  - Negative skin patch tests

**Treatment**

- **ACD**
  - Identify and avoid stimulating antigen to prevent occurrence; mild to moderate erythema requires class I-V topical corticosteroids; severe cases require oral prednisone or IM triamcinolone
  - Acute blisters and intense erythema effectively treated with cold, wet compresses and hydroxyzine or diphenhydramine for itching
- **ICD**
  - Identify and remove etiologic agent; use lubricating creams and barrier protection (gloves, creams, etc.); use potent topical class I corticosteroids in acute cases, prednisone if severe
  - Wash hands in cool water if exposed to irritant, and use cool compresses to treat vesicles/inflammation

**Prognosis**

- **ACD**
  - Symptomatic episodes will occur with each exposure after sensitization, so avoidance of allergen is essential to avoid recurrences
- **ICD**
  - Usually heals in 2 weeks upon removal of noxious stimulus, but chronic cases may take 6 weeks to heal
  - Only 1/3 of occupational cases achieve remission, while 2/3 require change of occupation

**MACROSCOPIC****General Features**

- **ACD**
  - Well-demarcated erythematous plaques with vesicles &/or dry scaling; lichenification; small, firm, round to flat papules; bullae; confluent erosions
- **ICD**
  - Spectrum of lesions ranges from sharply demarcated erythema with dry, cracked, fissured, crusted skin to lesions with vesicles and necrosis

**MICROSCOPIC****Histologic Features**

- ACD and ICD often not reliably distinguished due to overlap of histologic features
- **ACD**
  - Acute phase
    - Epidermal spongiosis often with vesicles at different levels of epidermis, exocytosis of lymphocytes and eosinophils, and microabscesses
    - Dermal edema and superficial perivascular lymphohistiocytic infiltrates with eosinophils
  - Subacute phase
    - Orthohyperkeratosis, focal parakeratosis, less epidermal spongiosis, mild epidermal hyperplasia, superficial dermal chronic inflammation
  - Chronic phase
    - Parakeratosis, psoriasiform epidermal hyperplasia, minimal spongiosis, papillary dermal fibrosis
    - Can show features similar to lichen simplex chronicus in most chronic form

- Special variants include pustular, purpuric, photoallergic, granulomatous, urticarial, and follicular
- **ICD**
  - Features vary with nature of irritant and duration of exposure
  - Highly concentrated irritants cause marked keratinocytic ballooning degeneration with variable necrosis ranging from single cells to confluent zones within upper epidermis
    - Mild spongiosis in adjacent epidermis and occasional dyskeratotic keratinocytes may be seen
    - Neutrophils are present in areas of epidermal necrosis and ballooning degeneration, and upper dermal infiltrates include neutrophils
    - Mild epidermal hyperplasia often seen, and psoriasiform hyperplasia may be present
  - Lower irritant concentrations cause spongiosis, perivascular infiltrates, and dermal edema similar to ACD
  - Pustular variant shows subcorneal vesicles with fibrinous exudate, debris, and neutrophils

**DIFFERENTIAL DIAGNOSIS****Allergic Contact Dermatitis**

- Spongiotic dermatitides appear similar with overlapping features giving nonspecific histologic differential diagnosis requiring clinical correlation
- Mycosis fungoides can resemble subacute and chronic phases of ACD
- Dermatophytosis can cause spongiotic dermatitis, so judicious use of special stains (PAS, GMS) to exclude fungus is necessary in some cases

**Irritant Contact Dermatitis**

- Shares features with some interface dermatitides and spongiotic dermatitides like ACD, spongiotic drug reaction, and nummular dermatitis
  - Clinical correlation helpful for diagnosis

**DIAGNOSTIC CHECKLIST****Pathologic Interpretation Pearls**

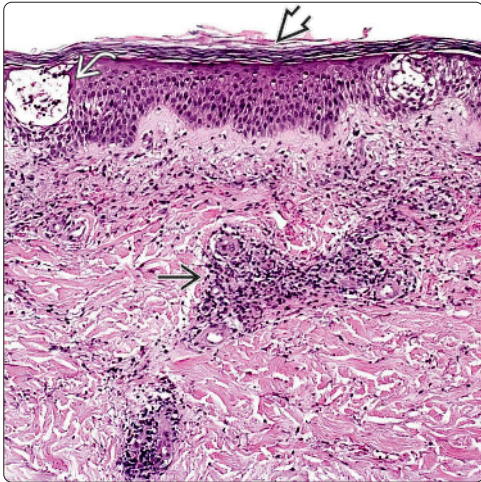
- ACD and ICD may appear histologically similar, which makes separation difficult
- Acute ACD shows prominent spongiosis with vesicles, neutrophils, and no necrosis, while chronic phase shows minimal spongiosis and may resemble lichen simplex chronicus
- ICD shows epidermal necrosis, dyskeratotic keratinocytes, and less spongiosis
- Clinical correlation is helpful for proper diagnosis

**SELECTED REFERENCES**

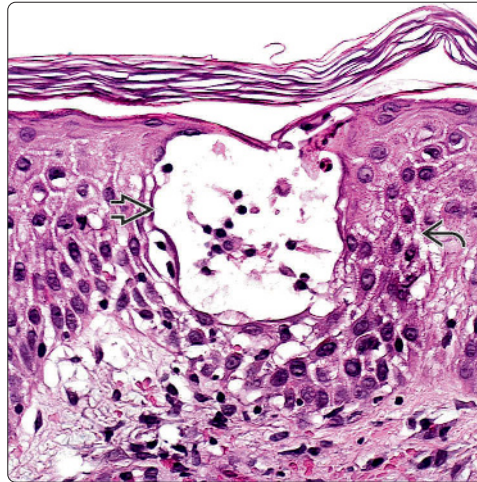
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**Acute Spongiotic Dermatitis With Microvesicles**

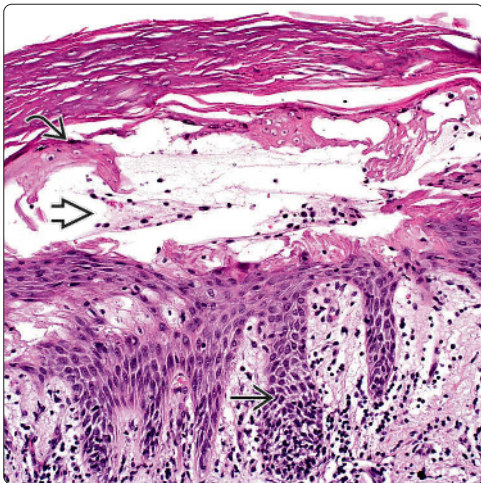


**Hallmark of Acute Spongiosis: Spongiotic Microvesiculation**

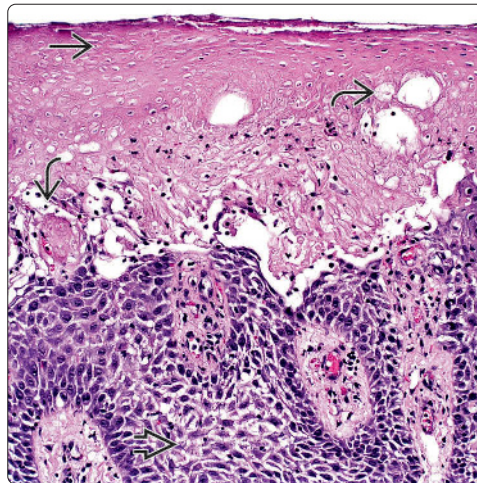


(Left) Acute ACD demonstrates prominent epidermal spongiosis with vesiculation [X], "basket weave" cornified epidermal layer showing compact orthohyperkeratosis [X], lymphocyte exostosis, and dermal perivascular lymphohistiocytic inflammation with eosinophils [X]. (Right) Prominent spongiosis [X] and resultant spongiotic microvesiculation [X] are characteristic expressions of intercellular edema that serve as hallmarks of acute ACD.

**Superficial Epidermal Necrosis in Irritant Contact Dermatitis**

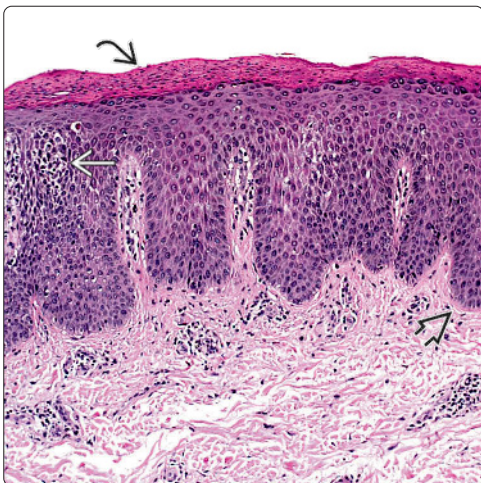


**Epidermal Necrosis With Spongiosis in Irritant Contact Dermatitis**

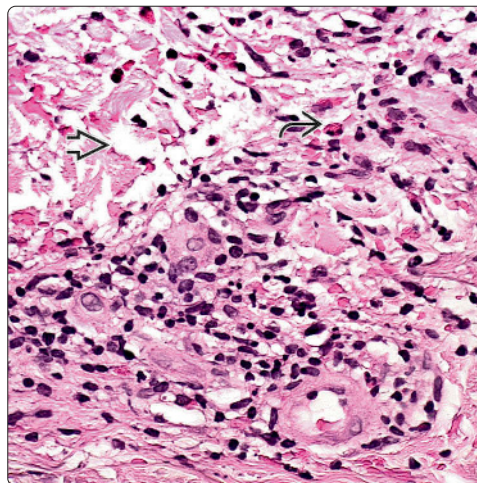


(Left) This example of irritant contact dermatitis shows superficial epidermal necrosis [X] with ballooning degeneration, edema, and vesicle formation [X] along with spongiosis [X] and mixed inflammatory infiltrates with neutrophils. (Right) Irritant contact dermatitis due to chemical irritant exposure can result in confluent superficial zones of epidermal necrosis [X] with edema and ballooning degeneration [X], epidermal spongiosis [X], and variable mixed inflammation.

**Subacute Spongiotic Dermatitis With Mild Spongiosis**



**Eosinophils and Edema in Allergic Contact Dermatitis**



(Left) Subacute to chronic ACD shows compact orthohyperkeratosis with parakeratosis [X], mild spongiosis [X], and psoriasiform epidermal hyperplasia [X] with a retained granular layer. At the extreme chronic end of the spectrum, there can be absent spongiosis, prominent psoriasiform hyperplasia, and dermal fibrosis mimicking lichen simplex chronicus. (Right) Close inspection of the dermis confirms the presence of eosinophils [X] and edema [X].



# Nummular Eczema

## KEY FACTS

### TERMINOLOGY

- Form of eczema that is distinct from other forms of eczema because of its sharply defined border and often coin-like/circular shape
  - Nummular means coin-like and comes from Latin word nummus, which means small coin

### CLINICAL ISSUES

- Usually occurs in adults
- Occurs as sharply demarcated, circular, erythematous patch or plaque that occurs on any part of body but prefers lower extremities, upper extremities, and torso
- Dorsal (extensor) surfaces of extremities and back are most common sites
- Plaques may be quite small (quarter sized) or as large as palm of hand
- Usually pruritic
- Usually chronic disease commonly with relapses and remissions

### MICROSCOPIC

- General spongiotic pattern
- Spongiosis ranges from microvesicle formation (acute lesions) to minimal (chronic lesions)
  - Amount of spongiosis depends on clinical duration of lesions
- Superficial perivascular lymphohistiocytic infiltrate with eosinophils
- Epidermal acanthosis is present in more chronic lesions

### TOP DIFFERENTIAL DIAGNOSES

- Contact dermatitis
- Id reaction
- Dyshidrotic dermatitis
- Atopic dermatitis

### DIAGNOSTIC CHECKLIST

- Can mimic other spongiotic processes histopathologically
- Clinical correlation is necessary for accurate diagnosis

Circular ('Coin-Shaped') Exudative Lesion



*Oval exudative crusted dermatitis on the upper outer arm in a case of nummular eczema is seen here. Note the well-demarcated edge with oozing and crusting but no scaling and no elevated edge with clearing center.*

## TERMINOLOGY

### Synonyms

- Nummular dermatitis
- Discoid eczema
- Papulovesicular eczema
- Orbicular eczema

### Definitions

- Form of eczema that is distinct from other forms of eczema because of its sharply defined border and often coin-like/circular shape
  - Most other forms of eczema characteristically have indistinct outline
  - Nummular means coin-like and comes from Latin word nummus, which means small coin

## ETIOLOGY/PATHOGENESIS

### Unknown

- Several factors have been proposed in pathogenesis
  - Dry skin
  - Emotional stress
  - Stasis
  - Atopic dermatitis in childhood

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - ~ 2 in 1,000
- Age
  - Usually occurs in adults
    - Bimodal peaks in 6-7th decade of life (most common) and 2nd-3rd decade of life
  - Rare in children
- Sex
  - Most studies report slight male predominance
- Ethnicity
  - No racial predilection has been reported
- Seasonal variation
  - Lesions often have peak frequency in winter
  - Summer may also worsen lesions especially in men

### Presentation

- Occurs as sharply demarcated, circular, erythematous patch or plaque that occurs on any part of body but prefers lower extremities, upper extremities, and torso
  - Dorsal (extensor) surfaces of extremities and back are most common sites
  - Dorsal (extensor) surfaces of hands are also commonly involved
- Plaques may be quite small (quarter-sized) or as large as palm of hand
  - Average size is around size of silver dollar
- Usually pruritic
- May be solitary or multiple, can be widespread

### Treatment

- Drugs
  - Emollients are first line

- Topical corticosteroids, tacrolimus, or pimecrolimus can also be used
- In severe or refractory cases, systemic corticosteroids may be used
- Antihistamines can relieve pruritus

### Prognosis

- Usually chronic disease commonly with relapses and remissions
  - Lesions may also persist for long periods

## MICROSCOPIC

### Histologic Features

- General spongiotic pattern
- Acute lesions show
  - Superficial perivascular lymphohistiocytic infiltrate with eosinophils
  - Abundant spongiosis with microvesicle formation
  - Difficult to differentiate from other acute spongiotic/eczematous processes
- Subacute lesions show
  - Superficial perivascular lymphohistiocytic infiltrate + eosinophils
  - Acanthosis with slight psoriasiform epithelial hyperplasia
  - Mild spongiosis ± parakeratosis
- Chronic lesions
  - Hyperkeratosis, parakeratosis, and acanthosis
  - Mild spongiosis with lymphocyte exocytosis
  - Superficial perivascular lymphohistiocytic + eosinophils
  - Difficult to distinguish from other spongiotic/eczematous processes

## ANCILLARY TESTS

### Histochemistry

- PAS should always be considered on any spongiotic process to rule out dermatophyte infection
  - Careful scrutinization of stratum corneum for organisms can also suffice

### Patch testing

- Should be considered in severe or persistent disease to exclude contact allergens

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

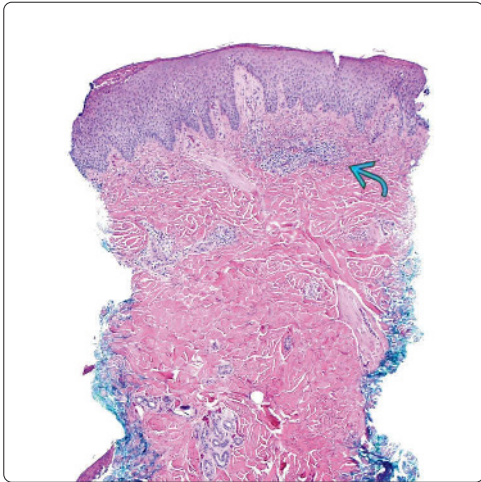
- Other spongiotic/eczematous processes
  - Contact dermatitis
    - Can be indistinguishable histopathologically
    - Lacks sharply defined, circular border
    - Often asymmetric and typically forms streaks or geometric shapes
  - Id reaction
    - Tends to be drier and very diffuse
    - No distinct circles clinically
    - Very symmetric (nummular may or may not be)
    - Histopathologically can be indistinguishable
- Dyshidrotic dermatitis
  - Can ooze and crust, but primary lesion is vesicle



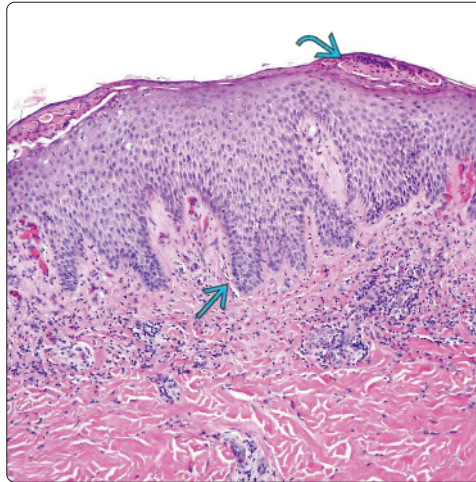
# Nummular Eczema

- Typically palms, soles, sides of fingers, and sides of toes
  - Histopathologically can be indistinguishable, but typically dyshidrosis shows spongiotic pattern limited to acral skin
  - Atopic dermatitis
    - Can be indistinguishable histopathologically
    - Often affects younger patients
    - Typically lichenified clinically
  - Dermatophytosis
    - Fungal hyphae present in stratum corneum
      - Can be highlighted with PAS or other fungal stain
    - Careful search for fungal hyphae within stratum corneum or PAS stain is warranted on all cases with spongiotic pattern
      - Treatment differs widely, and steroids will worsen disease
  - Pityriasis rosea
    - Clinically doesn't itch
    - Clinically diffuse hypopigmentation often involving upper trunk with very fine adherent scale
    - Histopathologically shows gently undulating epidermis with parakeratotic mounds and spongiosis
  - Seborrheic dermatitis
    - Usually in seborrheic areas
      - Intertriginous areas and folds, scalp, and forehead
    - Fine nonadherent scale that is greasy rather than dry
    - Typically shows parakeratosis at lips of follicular ostia
      - Spongiosis typically involves hair follicle epithelium
  - Stasis dermatitis
    - Clinically localized below knee on lower legs and ankles (typically medial malleolus)
      - Lower legs and ankles (typically medial malleolus)
    - Tends to be symmetric (both legs) and on large area
      - Nummular eczema is asymmetric, typically circular with multiple spots
    - Reddish-brown pigmentation is characteristic
      - Not seen in nummular eczema
  - Spongiotic drug eruption
    - Very uncommon type of drug eruption
    - Symmetric clinically
    - Typically occurs between 2-14 days after drug initiation
    - Large confluent areas, typically symmetric, no discrete circles (typically diffuse)
- ## Clinical
- Dermatophytosis
    - Clear in center (vs. nummular dermatitis)
    - Lesions spread concentrically
      - Nummular lesions attain full size immediately
    - Rarely oozes and crusts (vs. most cases of nummular eczema that ooze and crust)
    - Both pruritic
    - Commonly intertriginous
      - Nummular eczema is extensor disease
  - Psoriasis (especially guttate)
    - Almost never itches
    - Lesions are papulosquamous (elevated and with scale)
    - Typically no atopic history (vs. nummular eczema)
      - Not uncommon to have family history of psoriasis
  - More numerous lesions that are typically smaller
  - Allergic contact dermatitis
    - Oozing and crusting can be similar
    - Streaks and can have large blisters
    - Geometric shapes and asymmetry typically
  - Atopic dermatitis
    - Lichenified clinically
    - Dry dermatitis (typically no oozing or crusting)
    - More chronic (not sudden as in nummular eczema)
  - Stasis dermatitis
    - Localized below knee
    - Reddish-brown hyperpigmentation is characteristic
    - Associated with edema or venous disease (varicosities)
    - Typically affects older age group
  - Neurodermatitis (lichen simplex chronicus)
    - Not usually symmetric
    - Often just a few areas involved (areas within reach of patient)
      - Often in butterfly distribution with central areas where they can't reach
    - Linear scratches and excoriations typically present
    - Around edge are papules that coalesce into large plaques
    - Oozing and crusting typically not present
    - Itching is typically paroxysmal
    - Characteristically heals with hypopigmented scars
      - Eczema typically does not scar
- ## DIAGNOSTIC CHECKLIST
- ### Clinically Relevant Pathologic Features
- General spongiotic pattern
    - Can mimic other spongiotic processes
    - Clinical correlation is necessary for accurate diagnosis
- ## SELECTED REFERENCES
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**Slight Psoriasiform Epithelial Hyperplasia**

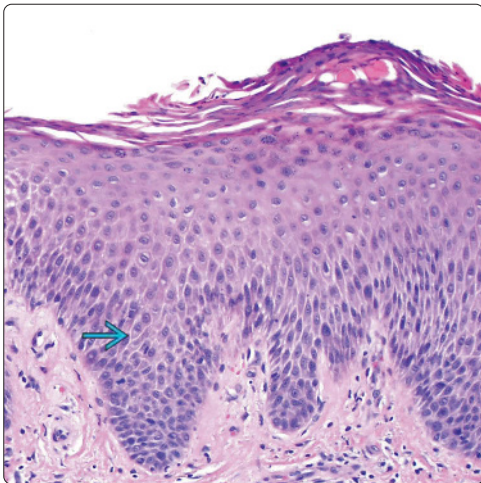


**Subacute Spongiotic Dermatitis**

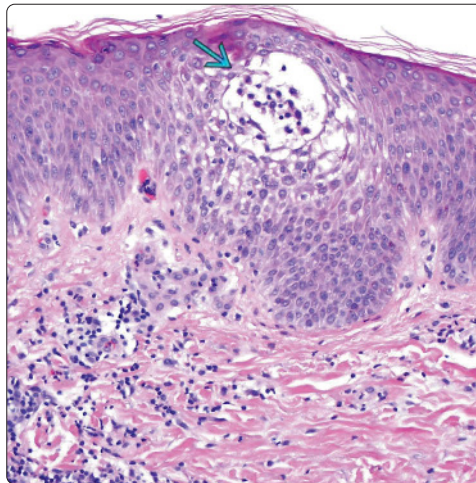


(Left) A low-power view of a case of nummular eczema demonstrates an acanthotic epidermis with slight psoriasiform epithelial hyperplasia with a superficial lymphohistiocytic infiltrate. (Right) This example of a subacute lesion of nummular eczema demonstrates a slight spongiotic dermatitis with psoriasiform hyperplasia and some serum within the stratum corneum. The serum represents prior edema that has been extruded out through the epidermis.

**Mild Spongiosis, Parakeratosis and Serum**

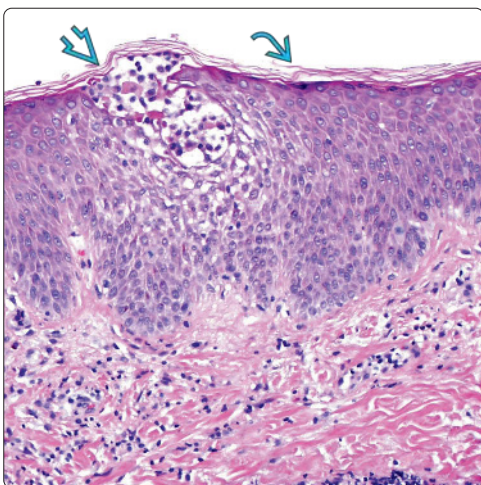


**Langerhans Cell Microgranuloma**

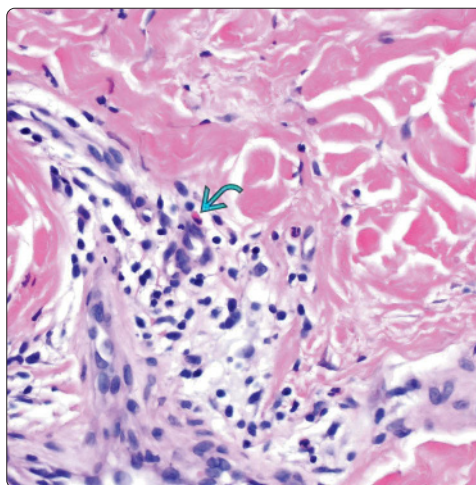


(Left) In subacute lesions of nummular dermatitis, spongiosis (seen here as white spaces between keratinocytes) is mild, and overlying parakeratosis and serum crust are often present. (Right) A Langerhans cell microgranuloma is seen here in a case of nummular eczema. Langerhans cell microgranulomas can be seen in all types of spongiotic processes and are not specific for any one process. Note the acuteness of this nummular lesion with the "basket weave" stratum corneum.

**Acute Spongiotic Dermatitis**



**Lymphohistiocytic Infiltrate With Rare Eosinophils**



(Left) This case of acute nummular dermatitis demonstrates another Langerhans cell microgranuloma with significant spongiosis surrounding and a "basket weave" stratum corneum. (Right) The superficial lymphohistiocytic infiltrate often has occasional eosinophils. Eosinophils are not a prerequisite for the diagnosis, but most spongiotic processes should have occasional eosinophils if biopsies are scrutinized enough.



## Asteatotic Eczema

## KEY FACTS

## TERMINOLOGY

- Eczema craquelé
- Winter itch
- Xerosis

## CLINICAL ISSUES

- Preferentially affects shins of elderly patients during winter months
- Presents as dry skin with fine scale and cracks, which resemble dry riverbed

## MICROSCOPIC

- Spongiosis of varying degrees
  - Acute lesions have more spongiosis
  - Chronic lesions have less spongiosis
- Exocytosis of varying degrees
- Acanthosis of varying degrees
  - Acute lesions have less acanthosis
  - Chronic lesions have more spongiosis

## TOP DIFFERENTIAL DIAGNOSES

- Atopic dermatitis
  - Clinically follows specific patterns of involvement from extensor to flexural over time in childhood to more focal locations in adults
  - Histopathology can be indistinguishable
- Stasis dermatitis
  - Clinically preferentially affects lower extremities of elderly or those with poor circulation
  - Histopathology shows prominent vascular components with adjacent hemosiderin deposition
- Allergic contact dermatitis
  - Clinically shows geographic lesions where contactant was in touch with skin
  - Histopathology can be indistinguishable, but Langerhans cell microgranulomas can be clue

## Pseudolchthyosis of Asteatotic Eczema

(Left) Shins of a middle-aged man during the winter season exhibit pseudoichthyosis-like scale [E] and on a background of xerotic skin. Focal patches of erythema [E] are from excoriations. (Courtesy E. Lilly, MD.) (Right) Close-up of the shin exhibits what looks like a dry riverbed type of xerotic scale with interlocking superficial cracks in the epidermis. (Courtesy E. Lilly, MD.)

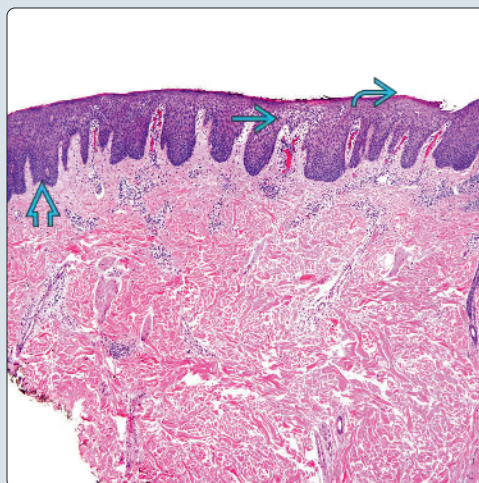


## Dried Riverbed Clinical Appearance

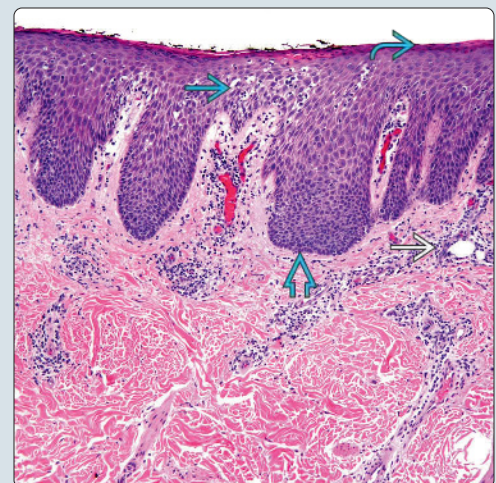


## Subacute Spongiotic Dermatitis

(Left) Low-power image shows the subacute stage of a spongiotic dermatitis with hyperkeratosis [E], epidermal hyperplasia [E], and focal spongiosis [E] of the keratinocytes. (Courtesy S. Wenson, MD.) (Right) High-power image shows the subacute stage of a spongiotic dermatitis with hyperkeratosis [E], epidermal hyperplasia [E], and focal spongiosis [E] of the keratinocytes. A nonspecific superficial perivascular lymphocytic infiltrate [E] is also seen. (Courtesy S. Wenson, MD.)



## Spongiosis and Superficial Perivascular Infiltrate





## TERMINOLOGY

### Synonyms

- Eczema craquelé
- Winter itch
- Dry skin
- Xerosis

### Definitions

- Pruritic type of eczema that preferentially affects lower extremities of elderly patients, especially in cold climates

## CLINICAL ISSUES

### Presentation

- Presents as dry skin with fine scale and cracks, which resemble dry riverbed
- Preferentially affects shins but can occur anywhere
- Elderly tend to be affected more, especially in winter months when humidity is low, people take hot showers ( $\pm$  use of soaps), when they are exposed to dry winter air and dry indoor heat

### Treatment

- Options, risks, complications
  - Decreased duration and temperature of showers
  - Limit use of gentle soaps to intertriginous areas and hands only
  - Pat skin dry after showering, then apply cream or ointment moisturizer
  - For recalcitrant cases not responding to emollients, topical steroids are great options

### Prognosis

- Generally most people improve with decreased drying habits, increased emollient use  $\pm$  use of topical steroids

## MICROSCOPIC

### Histologic Features

- Spongiosis is key feature along with varying degrees of parakeratosis, acanthosis, and lymphocytic exocytosis  $\pm$  superficial perivascular lymphocytic infiltrate
- Historically considered 1 of 3 possible states of activity depending on duration
  - Acute
    - Tends to have more prominent spongiosis (intercellular edema), which can produce intraepidermal spongiotic vesicles
    - Exocytosis present in variable amounts
    - Little to no acanthosis or parakeratosis
  - Subacute
    - Varying amounts of spongiosis, acanthosis, parakeratosis, and exocytosis somewhere between acute and chronic
  - Chronic
    - Tends to be more acanthotic with compact hyperkeratosis
    - Less spongiosis compared with acute and subacute cases

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Atopic dermatitis
  - Part of eczematous dermatitis spectrum with variable amounts of hyperkeratosis, acanthosis, spongiosis, and superficial perivascular lymphocytic infiltrate
  - Eosinophils can be present but tend not to be prominent
- Stasis dermatitis
  - More prominent vascular proliferations, sometimes glomeruloid in appearance in superficial to mid dermis
  - More hemosiderin deposition
- Allergic contact dermatitis
  - Features similar to eczema, but eosinophils tend to be more prominent in number

### Clinical

- Atopic dermatitis
  - Depending upon patient's age, distribution pattern is helpful
  - Infants: Scalp, cheeks, extensor surfaces, sparing diaper area
  - Children: Tends to involve surfaces of neck, wrists, elbows, knees, ankles
  - Adults: Tends to be more localized in distribution like flexural surfaces, hands, eyelids, nipples
- Stasis dermatitis
  - Preferentially affects lower extremities of elderly who have poor circulation
  - Can appear bronze or pigmented over shins; ulceration can happen in more severe cases
- Allergic contact dermatitis
  - Often occurs after exposure to specific culprit allergen, so thorough history of potential new exposures, changes in environment, or medications is imperative
  - Can occur in specific pattern like photodistribution, asymmetric, phytophoto, etc.

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Presents as dry skin with fine scale and cracks, which resemble dry riverbed

### Pathologic Interpretation Pearls

- Spongiosis and exocytosis

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# Dyshidrotic Eczema

## KEY FACTS

### TERMINOLOGY

- Subtype of eczema that occurs as vesiculopustules on hands, feet, fingers, &/or toes
- Synonyms include dyshidrosis, pompholyx, palmoplantar eczema

### CLINICAL ISSUES

- Occurs more commonly in warmer weather and often at intervals
  - Intervals can be regular or irregular and can be separated by several weeks, months, or even years
- Presents as sudden onset of numerous deep-seated pruritic crops of clear, sago grain-like vesicles on palms &/or soles
  - Often symmetric
- Mild cases often involve lateral fingers
- Scaling, fissures, and lichenification can ensue later

### MICROSCOPIC

- Acute lesions

- Spongiosis with exocytosis of lymphocytes
- Intraepidermal vesiculation
- Superficial lymphohistiocytic infiltrate  $\pm$  eosinophils
- Chronic lesions
  - More acanthosis and parakeratosis
  - Spongiosis diminished and vesiculation absent
  - Superficial lymphohistiocytic infiltrate  $\pm$  eosinophils

### TOP DIFFERENTIAL DIAGNOSES

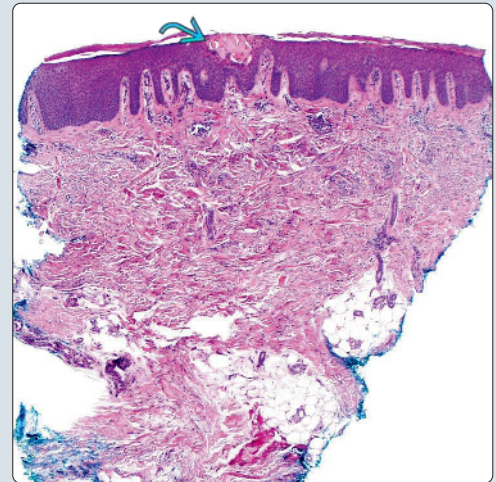
- Other spongiotic dermatitides
  - Include allergic contact dermatitis, nummular dermatitis, id reaction, and atopic dermatitis
    - More easily distinguished clinically
- Bullous arthropod bite reaction
- Bullous dermatophytosis
- Photoallergic contact dermatitis

#### Deep-Seated Vesicles Over Fingertips

(Left) Deep-seated vesicles over the fingertips, some of which have become hemorrhagic crusts, are seen in a patient with dyshidrosis. (Right) Low-power view of a case of dyshidrosis demonstrates a nonspecific spongiotic pattern with microvesicle formation as well as a superficial perivascular infiltrate. A thick, compact stratum corneum indicates that this is from acral skin.



#### Spongiotic Dermatitis on Acral Skin

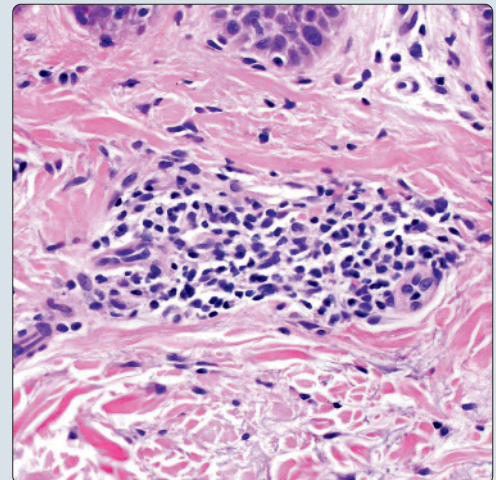


#### Microvesicle Present on Acral Skin

(Left) A small microvesicle is seen with exocytosis of lymphocytes, surrounding spongiosis, and a superficial perivascular lymphohistiocytic infiltrate. Note the thickened, compact stratum corneum of acral skin. (Right) A high-power view of dyshidrosis demonstrates a nonspecific superficial perivascular lymphohistiocytic infiltrate. Eosinophils may or may not be present.



#### Superficial Perivascular Lymphohistiocytic Infiltrate



## TERMINOLOGY

### Abbreviations

- Dyshidrotic eczema (DE)

### Synonyms

- Dyshidrosis
- Pompholyx
- Palmoplantar eczema

### Definitions

- Subtype of eczema that occurs as vesiculopustules on hands, feet, fingers, &/or toes

## ETIOLOGY/PATHOGENESIS

### Unknown

- However numerous things have been reported to worsen or induce lesions
  - Palmoplantar hyperhidrosis
  - Hot climate
  - Psychological stress
- Allergies to the following have also been reported to induce or exacerbate lesions
  - Nickel
  - Drugs

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Occurs more commonly in warmer weather and often at intervals
    - Intervals can be regular or irregular and can be separated by several weeks, months, or even years

### Presentation

- Sudden onset of numerous deep-seated pruritic crops of clear, sago grain-like vesicles on palms &/or soles
  - Often symmetric
- Mild cases often involve lateral fingers
- Severe cases can form large coalescing bullae
- Scaling, fissures, and lichenification can ensue later

### Treatment

- Drugs
  - Topical calcineurin inhibitors
  - Steroid or tacrolimus creams
- In severe or recalcitrant cases, other treatments can be tried, such as
  - Systemic steroids
- Narrow-band UVB can also be used for recalcitrant cases

### Prognosis

- Generally good
  - Although disease is benign, severe cases can be debilitating to some patients and significantly affect quality of life

## MICROSCOPIC

### Histologic Features

- Acute lesions

- Spongiosis with exocytosis of lymphocytes
- Intraepidermal vesiculation
- Superficial perivascular lymphohistiocytic infiltrate ± eosinophils
- Chronic lesions
  - More acanthosis and parakeratosis
  - Spongiosis is diminished
  - Vesiculation typically absent
  - Superficial perivascular lymphohistiocytic infiltrate ± eosinophils

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Other spongiotic dermatitides
  - Allergic contact dermatitis
    - Can be indistinguishable histopathologically
    - Distinguished clinically
      - ◻ Lesions are sharply confined within areas where causative agent was in contact with skin
  - Nummular dermatitis
    - Can be indistinguishable histopathologically
    - Clinically, shows tense vesicles in coin-like clusters
  - Id reaction
    - Can be indistinguishable histopathologically
    - Clinically, widespread symmetric eruption of tense vesicles that can be pompholyx-like
      - ◻ Lesions tend to be transient
      - ◻ Usually associated with tinea pedis in this instance
      - ◻ Clinically, can also be more generalized intensely pruritic papulovesicular eruption that can involve multiple sites
  - Atopic dermatitis
    - Can be indistinguishable histopathologically
    - Lesions typically develop in infancy and are more widespread (not limited to palms and soles)
- Bullous bite reaction
  - Infiltrate is typically deeper and wedge-shaped and often has more eosinophils
    - Deep, interstitial eosinophils are highly suggestive
- Bullous dermatophytosis
  - Hyphae present within stratum corneum
    - Can be highlighted with PAS stain
- Photoallergic contact dermatitis
  - Typically deeper lymphohistiocytic infiltrate around superficial and deep vessels
  - Occasionally necrotic keratinocytes may be present

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## Id Reaction

## KEY FACTS

## TERMINOLOGY

- Generalized, eczematous, type IV delayed hypersensitivity skin reaction that occurs at sites distant to previously localized dermatitis

## CLINICAL ISSUES

- Most commonly involves forearms, legs, and trunk
- Clinical appearance is typically symmetric widespread papules that are extremely itchy
- Occurs 1-2 weeks after primary infection/dermatitis occurs or worsens
- Vigorous treatment of primary lesions/dermatitis is key for treatment

## MICROSCOPIC




- Early lesions
  - Prominent spongiosis ± microvesicle formation
  - Prominent lymphocyte exocytosis

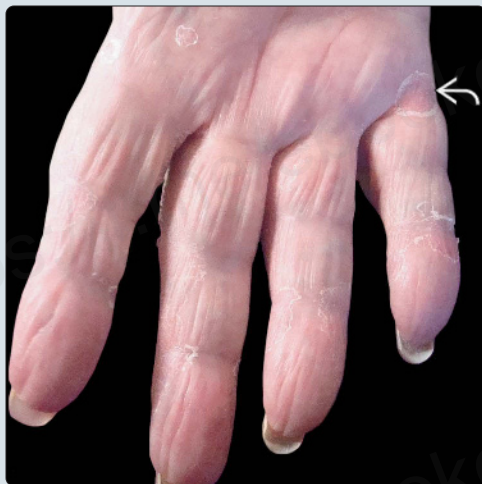
- Superficial perivascular lymphohistiocytic infiltrate + eosinophils
- Late lesions
  - Regularly elongated rete ridges
  - Less spongiosis, less lymphocyte exocytosis
  - Hyperkeratosis, with wedge-shaped hypergranulosis + parakeratosis

## TOP DIFFERENTIAL DIAGNOSES

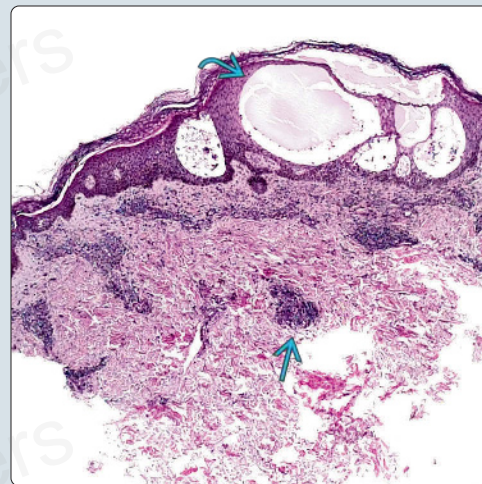
- Contact dermatitis
- Nummular eczema
- Dyshidrotic dermatitis (pompholyx)
- Viral exanthem
- Spongiotic drug eruption

Desquamative Id Reaction




(Left) Patient with vesicular tinea pedis and a desquamative  nonspecific id reaction on the flexor fingers and palm. (Right) This example of an id reaction shows a nonspecific acute spongiotic pattern with microvesicle formation  as well as a superficial lymphohistiocytic infiltrate . Occasional eosinophils were present on higher power.



Acute Spongiosis With Microvesicle Formation

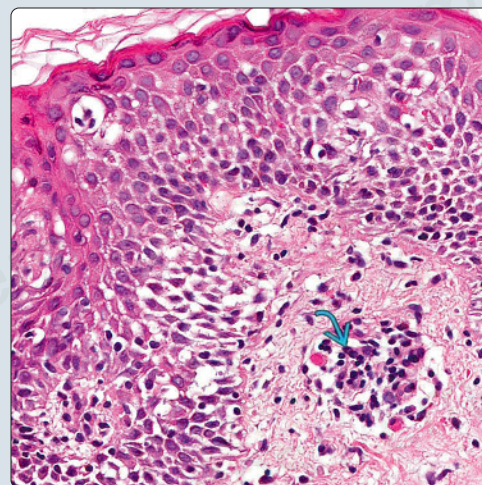


Spongiosis With Superficial Perivascular Infiltrate

(Left) Low-power view of an id reaction demonstrates a nonspecific spongiotic pattern without microvesicle formation and a superficial perivascular infiltrate . There is also focal parakeratosis . (Right) This example of an id reaction demonstrates mild to moderate spongiosis with a superficial perivascular lymphohistiocytic infiltrate and an occasional eosinophil .



Spongiotic Dermatitis With Occasional Eosinophils



## TERMINOLOGY

### Synonyms

- Hypersensitivity reaction
- Eczematid or autoeczematization
- Autosensitization dermatitis
- Disseminated secondary eczema
- Isomorphic response
- Dermatophytid, pediculid, scabid, virusid, and bacterid when associated with corresponding etiologic factor/infectious agent

### Definitions

- Generalized, eczematous, type IV delayed hypersensitivity skin reaction that occurs at sites distant to previously localized dermatitis

## ETIOLOGY/PATHOGENESIS

### Exact Cause Unknown

- Several theories
  - Immune response to circulating cytokines or infectious organisms
    - Dissemination of infectious antigens with secondary response
    - Hematogeneous dissemination of inflammatory cytokines from primary site
  - Abnormal immune recognition of autologous skin antigens
  - Increased stimulation of normal T cells by altered skin constituents
  - Lowering of "irritation threshold"

## CLINICAL ISSUES

### Epidemiology

- Age
  - Can occur at any age
- Sex
  - No predilection
- Ethnicity
  - No predilection

### Site

- Most commonly involves forearms, legs, and trunk

### Presentation

- Clinical appearance is typically symmetric widespread papules that are extremely itchy
  - Occurs 1-2 weeks after primary infection/dermatitis occurs or worsens
  - Lesion can also occasionally be papulovesicular or eczematous
    - Exception rather than rule
  - Vesicles on hands &/or feet may appear mimicking pompholyx
  - Very nonspecific clinically
- Occasionally patient may feel general malaise
  - Loss of appetite, fever

### Treatment

- Options, risks, complications

- Wound care may be needed for weeping eczematous lesions
- Drugs
  - Antihistamines may help with itch &/or for sedative purposes at night
  - Topical or systemic steroids may be needed to quell dermatitis
  - Potassium permanganate may be given for weeping lesions to prevent infection
- Vigorous treatment of primary lesions/dermatitis is tantamount
  - May require systemic therapy depending on etiology or severity of disease

### Prognosis

- Usually good with appropriate recognition and treatment

## MICROSCOPIC

### Histologic Features

- General spongiotic pattern
  - Spongiosis ± microvesicle formation (typically in early lesions only)
  - Lymphocyte exocytosis
  - Superficial perivascular lymphohistiocytic infiltrate ± eosinophils
    - Eosinophils may be less conspicuous than in other spongiotic dermatitides
- Early lesions
  - Spongiosis more prominent, and microvesicles may be present
  - Lymphocyte exocytosis is more prominent
- Late lesions
  - Regularly elongated rete ridges
  - Less spongiosis and less lymphocyte exocytosis
- Later lesions can be indistinguishable from lichen simplex chronicus

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Contact dermatitis
  - More eosinophils and Langerhans cell microgranulomas
  - Clinically limited to areas where contactant touched skin
- Nummular eczema
  - Clinically circular lesion without clearing in center
- Dyshidrotic dermatitis (pompholyx)
  - Dyshidrotic dermatitis is limited to hands and feet (no widespread eruption as in id reaction)
- Viral exanthem
  - Clinically symmetric, diffuse redness
- Spongiotic drug eruption
  - Clinical history of drug exposure
  - No history of localized, preceding inflammation (as would be seen in id reaction)

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## KEY FACTS

### TERMINOLOGY

- Erythema and scale on seborrheic distribution (malar region, scalp, external ear canal, nasolabial folds, eyebrow, ears, and chest)

### CLINICAL ISSUES

- Scaly and greasy papules and plaques in seborrheic distribution
- Infancy, puberty, and peak at middle age

### MICROSCOPIC

- Spongiosis (acute or chronic) in epidermis and follicular epithelium
- Mounds of scale crust at follicular ostia
- Neutrophils located at scale crust
- For chronic lesions, more psoriasiform epidermis

### TOP DIFFERENTIAL DIAGNOSES

- Psoriasis
  - More regular psoriasiform hyperplasia

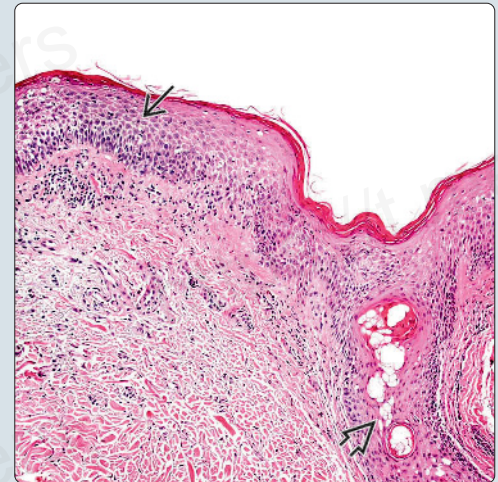
- Neutrophils in spinous layer of epidermis (Kogoj pustules)
- Contact dermatitis
  - More diffuse spongiosis
  - Clinically, not in seborrheic areas and more focal to the irritant
- Dermatophytosis
  - Hyphae seen in special stain such as PAS-D
- Discoid lupus
  - Superficial and deep perivascular and periadnexal inflammatory infiltrate
  - Interface changes (basal vacuolar alteration and necrotic keratinocytes) of epidermis
  - Increased dermal mucin
  - Thickened basement membrane

Greasy Fine Scale of Seborrheic Dermatitis

(Left) *Seborrheic dermatitis* presents in this patient as a papulosquamous dermatitis preferring the creases of the skin with greasy, fine, nonadherent scale on a pink base. (Right) Low-power view of seborrheic dermatitis shows spongiosis of the epidermis and follicular epithelium.

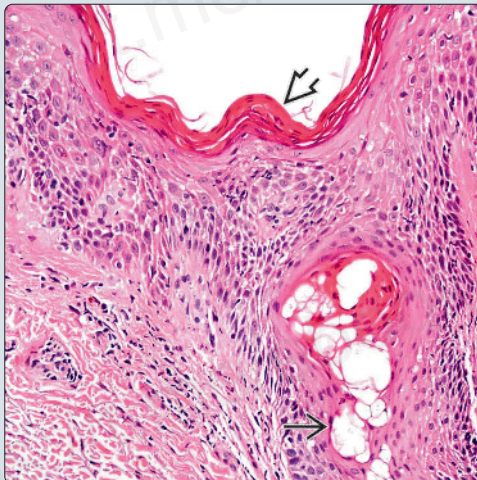


Follicular Spongiosis of Seborrheic Dermatitis

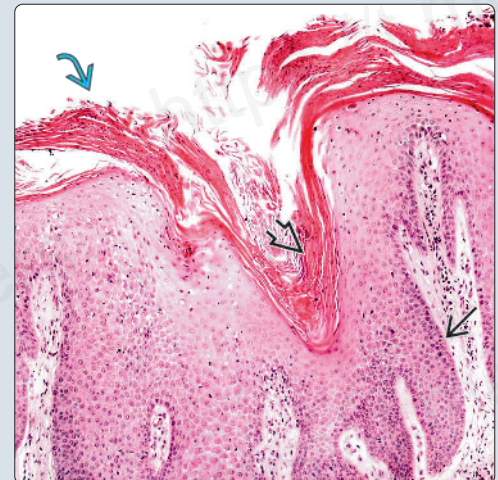


Parakeratosis and Follicular Spongiosis

(Left) Higher power view of seborrheic dermatitis shows parakeratosis in the follicular ostia and spongiosis of the follicular epithelium. (Right) A later lesion of seborrheic dermatitis demonstrates psoriasiform epidermal hyperplasia with parakeratosis in the follicular ostia. Often it occurs at the "lips" or at the edges of follicular ostia, as seen here.



Parakeratosis at "Lips" of Follicular Ostia





## TERMINOLOGY

### Abbreviations

- Seborrheic dermatitis (SD)

### Synonyms

- Seb derm
- Cradle cap in infants; dandruff (mild form of SD)

### Definitions

- Erythema and scale on seborrheic distribution (malar region, scalp, external ear canal, nasolabial folds, eyebrow, ears, and chest)

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- Possible link to *Malassezia furfur* or other *Malassezia* species such as *M. globosa* and *M. restricta*

### Unknown

- Thought to be dysfunction of sebaceous gland
- Possibly linked to *Malassezia (Pityrosporum)* species
- Possible link to UV exposure

### Disease Association

- Worse in HIV patients
- Can be seen in Parkinson disease, obesity, zinc deficiency, and chronic alcoholism
- Can be precipitated by lithium

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - High: 3-5% of general population
  - Up to 20% for dandruff
- Age
  - Infancy, puberty, and peak at middle age
- Sex
  - No predilection

### Site

- Malar region, scalp, external ear canal, nasolabial folds, eyebrow, ears, and chest ("seborrheic distribution")

### Presentation

- Scaly and greasy papules and plaques in seborrheic distribution

### Treatment

- Drugs
  - Shampoo
    - Salicylic acid
    - Tar
    - Selenium
  - Ketoconazole
  - Corticosteroids

### Prognosis

- Excellent
  - Benign condition

## MICROSCOPIC

### Histologic Features

- Spongiosis (acute or chronic) in epidermis and follicular epithelium
- Mounds of scale crust at follicular ostia
- Neutrophils located at scale crust
- For chronic lesions, more psoriasiform epidermis

## DIFFERENTIAL DIAGNOSIS

### Histologic Differential Diagnosis

- **Psoriasis**
  - More regular psoriasiform hyperplasia
  - Less spongiosis
  - Neutrophils in spinous layer of epidermis (Kogoj pustules)
  - More confluent parakeratosis (not restricted to follicular ostia)
  - Loss or decrease of granular layer
  - Dilated vessels in dermal papillae
- **Contact dermatitis**
  - More diffuse spongiosis
  - More dermal eosinophils
  - More confluent parakeratosis
  - No increase of Langerhans cells
  - Clinically, not in seborrheic areas and more focal to irritant
- **Dermatophytosis**
  - Hyphae seen in special stain such as PAS-D
  - Usually mounds of parakeratosis more diffuse and not localized to follicular ostia
- **Discoid lupus**
  - Superficial and deep perivascular and periadnexal inflammatory infiltrate
  - Interface changes (basal vacuolar alteration and necrotic keratinocytes) of epidermis
  - Thickened basement membrane
  - Hyperkeratosis and follicular plugging
  - Increased dermal mucin
  - In tumid lesions, there is epidermal atrophy

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## KEY FACTS

### TERMINOLOGY

- Common, self-limited, acute papulosquamous eruption of salmon-pink, oval lesions on trunk, neck, and proximal extremities

### CLINICAL ISSUES

- Flu-like prodrome may be reported 2-3 weeks before cutaneous findings
- "Herald patch" may appear days to weeks before other pityriasis rosea lesions
  - Pink to salmon-colored oval plaque with central fine scale and peripheral trailing collarette
- Generalized eruption
  - Numerous smaller (1-2 cm) pink or salmon-colored round to oval papules with characteristic collarette of scale
  - Trunk and proximal extremities most affected
  - Fir or Christmas tree pattern on posterior trunk

### MICROSCOPIC

- Histopathological features are nonspecific
- Focal spongiosis, patchy or diffuse parakeratosis, often forming angulated mounds
- Mild lymphohistiocytic perivascular and interstitial infiltrate in superficial dermis
- Red blood cell extravasation in upper dermis and often epidermis

### TOP DIFFERENTIAL DIAGNOSES

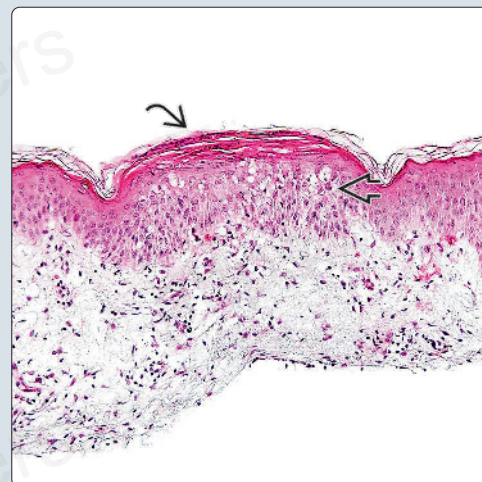
- Histologic differential diagnosis
  - Erythema annulare centrifugum
  - Pigmented purpuric dermatosis
  - Guttate psoriasis
- Clinical differential diagnosis
  - Pityriasis rosea-like drug eruption
  - Secondary syphilis
  - Guttate psoriasis

### Papulosquamous Eruption of Pityriasis Rosea

(Left) Classic distribution of pityriasis rosea (PR) shows small, pink or salmon-colored oval papules on the posterior trunk and proximal arms. The long axes of the oval papules follow skin tension lines, forming a Christmas tree pattern. (Right) This case of PR displays more prominent spongiosis underlying a focus of parakeratosis. The dermal lymphocytic infiltrate is sparse and interstitial, and red blood cell extravasation is present.

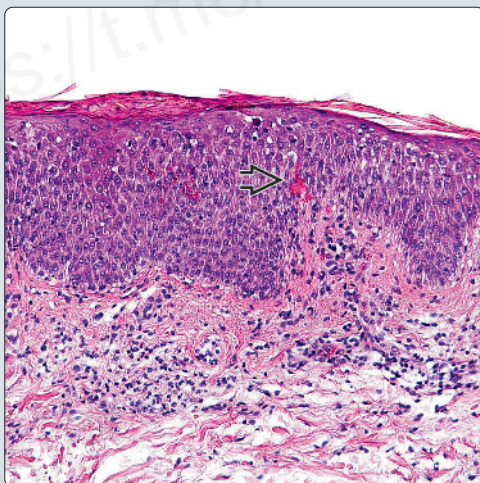


### Spongiosis With Parakeratosis

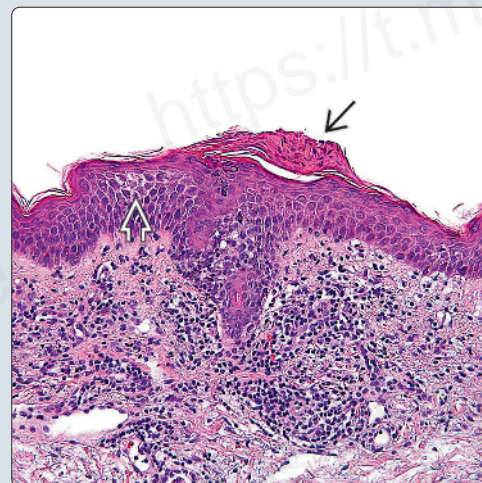


### Extravasated Erythrocytes

(Left) Extravasation and transepidermal elimination of red blood cells are not infrequent findings in PR. (Right) PR often shows a mound of parakeratosis with adjacent spongiosis within a slightly acanthotic epidermis. A perivascular lymphocytic infiltrate is present in the superficial dermis.



### Mounded Parakeratosis



## TERMINOLOGY

### Abbreviations

- Pityriasis rosea (PR)

### Synonyms

- Pityriasis rosea Gibert

### Definitions

- Common, self-limited, acute papulosquamous eruption of salmon-pink, oval lesions on trunk, neck, and proximal extremities

## ETIOLOGY/PATHOGENESIS

### Unknown

- Infectious etiology suspected
  - Supported by clustering of cases in communal living, history of preceding upper respiratory infection, and low frequency of recurrence
  - Recent focus on human herpesvirus (HHV)7 and HHV6
- PR-like reaction reported with graft-vs.-host reaction, bone marrow transplantation, acute myeloid leukemia, and Hodgkin disease

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Common
  - Seasonal variation, with highest prevalence in spring and fall
- Age
  - All ages can be affected, but majority of patients are between 10-35 years old
- Sex
  - Slightly more common in females

### Presentation

- Flu-like prodrome may be reported 2-3 weeks before cutaneous findings
- "Herald patch" may appear days to weeks before other PR lesions
  - Pink to salmon-colored oval plaque with central fine scale and peripheral trailing collarette
  - Size varies from 2-10 cm in diameter
  - Present in over 1/2 of cases
- Generalized eruption
  - Numerous smaller (1-2 cm) pink or salmon-colored round to oval papules with characteristic collarette of scale
  - Trunk and proximal extremities most affected
    - Typically spares face, palms, and soles
  - Fir or Christmas tree pattern on posterior trunk
    - Long axes of oval lesions follow Langer lines of cleavage
  - Eruption typically asymptomatic
    - Mild to severe pruritus may be reported
- Atypical forms
  - Papular, urticarial, erythema multiforme-like, vesicular, pustular, hemorrhagic, and purpuric variants have been reported

- "Inverse" variant with involvement of axillae, inguinal areas, and face

### Treatment

- No treatment necessary
  - Patient education and reassurance
- Pruritus: Can treat with topical antipruritic lotions, topical steroids, antihistamines
- Possible short-course systemic corticosteroids in severe cases
- Broadband UVB light treatments decrease severity but have not been shown to shorten duration of PR
- Acyclovir may shorten duration of eruption

### Prognosis

- Self-limited course
- Resolves spontaneously in 6-8 weeks
  - Rarely, cases persist for 5 months or longer
  - Recurrences are uncommon

## MICROSCOPIC

### Histologic Features

- Histopathological features are relatively nonspecific
  - Clinicopathologic correlation is necessary
- Focal spongiosis, rarely with spongiform vesiculation
- Patchy or diffuse parakeratosis, often forming mounds of parakeratosis
  - Granular layer frequently diminished beneath parakeratosis
  - Mound of parakeratosis may have angulated arrangement like the lid of a teapot
- Mild lymphohistiocytic perivascular and interstitial infiltrate in superficial dermis
- Red blood cell extravasation within upper dermis and often epidermis
- Variable acanthosis
- Dyskeratotic keratinocytes may be seen in 50% of cases

## DIFFERENTIAL DIAGNOSIS

### Histologic Differential Diagnosis

- Erythema annulare centrifugum (EAC)
  - Biopsy from advancing edge of EAC indistinguishable from PR
  - Well-demarcated "coat sleeve" superficial perivascular lymphohistiocytic infiltrate
- Pigmented purpuric dermatosis
  - Infiltrate concentrated around superficial capillaries (vs. postcapillary venules in PR)
  - Variable spongiosis and focal parakeratosis
  - Hemosiderin-laden macrophages in older lesions
- Guttate psoriasis
  - Foci of neutrophils within or atop mounds of parakeratosis
  - More sparse infiltrate, less spongiosis than PR
  - Few or no extravasated red blood cells

## SELECTED REFERENCES

1. Drago F et al: Pityriasis rosea: an update with a critical appraisal of its possible herpesviral etiology. *J Am Acad Dermatol*. 61(2):303-18, 2009



## KEY FACTS

### ETIOLOGY/PATHOGENESIS

- Develops secondary to longstanding venous insufficiency
- Increased intravascular pressure causes congestion and dilation of capillaries

### CLINICAL ISSUES

- Age
  - Middle-aged and elderly individuals
- Site
  - Distal extremities
    - Classically near medial malleolus and bilateral
- Appearance
  - Brown to black discoloration of affected areas
  - Erythematous, pruritic, scaly papules and plaques

### MICROSCOPIC

- Acanthosis with mild spongiosis
- Overlying hyperkeratosis with orthokeratosis or parakeratosis

- Proliferation of superficial dermal blood vessels
- Variable degree of fibrosis
- Red blood cell extravasation
- Variable amount of hemosiderin deposition

### TOP DIFFERENTIAL DIAGNOSES

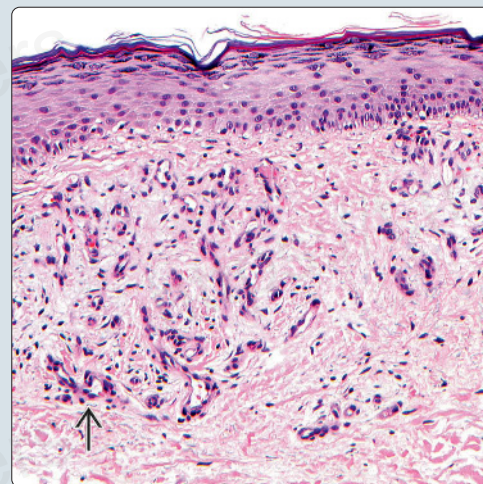
- Acroangiokeratosis
  - Considered severe variant of stasis dermatitis
- Kaposi sarcoma
  - Slit-like vessels that dissect through dermal collagen with extravasated erythrocytes
- Hemangioma
  - Localized vascular proliferation
- Angiosarcoma
  - Endothelial atypia and mitoses
- Chronic eczematous dermatitis
- Atrophie blanche (livedoid vasculopathy)

**Gray-Brown Brawny Scale Over Medial Ankle**

(Left) Brawny, gray-brown, adherent, dry scale over the medial ankle is the most common location for stasis dermatitis. Lower extremity is edematous with hyperpigmentation. (Right) Stasis dermatitis is characterized by a superficial dermal capillary proliferation

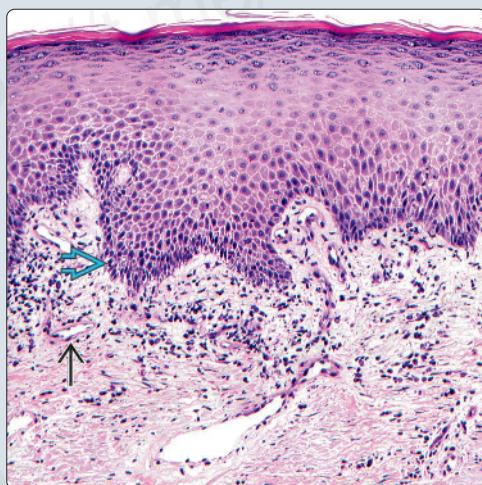


**Superficial Dermal Capillary Proliferation**

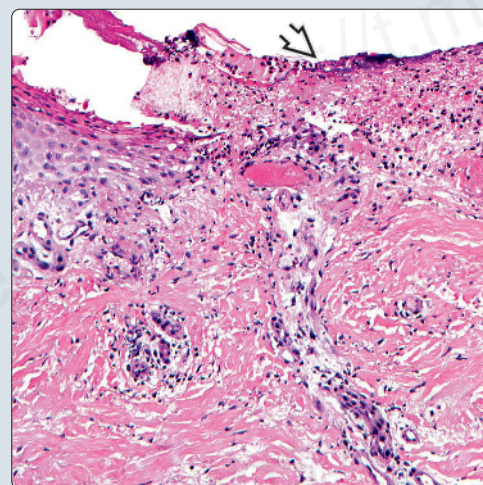


**Acanthosis, Spongiosis, and Dermal Capillary Proliferation**

(Left) Hyperkeratosis, acanthosis, and mild spongiosis are present with dermal capillary proliferation and mild chronic inflammation. (Right) There is ulceration overlying superficial capillary proliferation. Dermal fibrosis is increased, indicating an extended period of dermal injury.



**Stasis Ulcer With Fibrosis and Capillary Proliferation**



## TERMINOLOGY

### Synonyms

- Hypostatic dermatitis

### Definitions

- Hyperpigmentation primarily of distal extremities in patients with chronic venous incompetence

## ETIOLOGY/PATHOGENESIS

### Pathogenesis

- Develops secondary to longstanding venous insufficiency
  - Blood flow slows or becomes retrograde
- Increased intravascular pressure causes congestion and dilation of capillaries
  - Vascular sludging impairs adequate tissue oxygenation
    - Chronic ischemia
  - Damage of endothelium
    - Vascular leak and edema
    - Red blood cell extravasation
    - Hemoglobin is degraded, causing clinical hyperpigmentation
  - Microthrombi form, leading to focal necrosis and eventually ulceration
  - Chronic inflammation with deposition of fibrous tissue
    - Hardening of skin referred to as lipodermatosclerosis
    - Deranged cytokine cascades
    - Upregulation of transforming growth factor- $\beta$ , basic fibroblast growth factor, platelet-derived growth factor
    - Increased matrix metalloproteinases lead to dermal matrix degradation
  - Lipodermatosclerosis contributes to ulcer formation
    - Impairs wound healing
    - Increases susceptibility to infection

## CLINICAL ISSUES

### Epidemiology

- Age
  - Middle-aged and elderly individuals
- Sex
  - M:F = 1:1

### Site

- Distal extremities
  - Upper: Secondary to arteriovenous fistulas implanted for end-stage renal disease
  - Lower: Secondary to impaired venous flow due to congestive heart failure, diabetes mellitus, venous hypertension
  - Classically near medial malleolus and bilateral

### Presentation

- Appearance
  - Brown to black discoloration of affected areas
  - Erythematous, scaly papules and plaques
  - Presence of varicose veins is common
- Symptoms
  - Pruritus, tenderness

## Treatment

- Surgical approaches
  - Obliteration, stripping, or ligation of affected veins, valvular repair
- Drugs
  - Mild- to moderate-potency topical corticosteroids, topical antimicrobials, allogeneic cultured dermal substitute
- Patient based
  - Compression stockings &/or boots, leg elevation above level of heart, exercise
  - Soaking skin and using emollients to gently remove scale
- Treat underlying conditions

## Prognosis

- Common complications
  - Ulceration, cellulitis, contact dermatitis, autoeczematization, lipodermatosclerosis, poor wound healing

## MICROSCOPIC

### Histologic Features

- Acanthosis with mild spongiosis
- Overlying hyperkeratosis with orthokeratosis or parakeratosis
- Proliferation of superficial dermal blood vessels
- Variable degree of fibrosis
- Red blood cell extravasation
  - Variable amount of hemosiderin deposition

## DIFFERENTIAL DIAGNOSIS

### Histopathologic Differential Diagnosis

- **Acroangiodermatitis**
  - Vascular proliferation extends deeper than in stasis dermatitis
  - Venules and capillaries proliferate and are more tortuous and hypertrophic
- **Kaposi sarcoma**
  - Positive with HHV8 immunostain
  - Slit-like vessels that dissect through dermal collagen with extravasated erythrocytes
- **Hemangioma**
  - Localized vascular proliferation
- **Angiosarcoma**
  - Endothelial atypia and mitoses
- **Chronic eczematous dermatitis**
  - Spongiosis more prominent
  - May be superimposed on stasis dermatitis
- **Atrophie blanche (livedoid vasculopathy)**
  - Deposition of fibrinoid material in vessel walls
  - Fibrin thrombi in small vessels

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2. Palmer B et al: Acroangiodermatitis secondary to chronic venous insufficiency. *Cutis.* 86(5):239-40, 2010
3. Farage MA et al: Clinical implications of aging skin: cutaneous disorders in the elderly. *Am J Clin Dermatol.* 10(2):73-86, 2009



# Lichen Simplex Chronicus

## KEY FACTS

### TERMINOLOGY

- Various skin changes caused by chronic itching and scratching

### ETIOLOGY/PATHOGENESIS

- Pruritus
  - Underlying trigger for skin scratching
  - Number of conditions can cause pruritus: Other medical disorders, other dermatologic disorders, nerve proliferation, psychological disorders
  - Main dermatoses causing underlying pruritus: Atopic dermatitis, allergic contact dermatitis, insect bites, and stasis dermatitis

### CLINICAL ISSUES

- Circumscribed, erythematous, thickened, scaly papules or plaques with lichenification and excoriations
- Affected area often hyperpigmented
- Treatment

- Topical and intralesional glucocorticoids are mainstay

### MICROSCOPIC

- Hyperorthokeratosis with rare parakeratosis, hypergranulosis, and irregular acanthosis
- Papillary dermal fibrosis is characteristic feature
- Mixed perivascular inflammatory infiltrate

### TOP DIFFERENTIAL DIAGNOSES

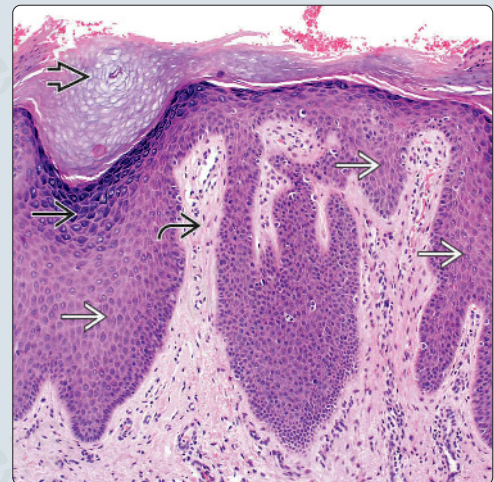
- Psoriasis
  - Hypogranulosis and regular acanthosis
  - Neutrophils often present in stratum corneum
- Chronic spongiotic dermatitis
  - More prominent intercellular edema with lymphocytic infiltrate
- Seborrheic dermatitis
  - More likely to have neutrophils in stratum corneum, specifically at edges of follicular ostia

### Lichenified Plaques

(Left) Lichen simplex chronicus often presents as erythematous and excoriated papules and plaques. (Right) This low-power image demonstrates hyperkeratosis [box], hypergranulosis [box], and irregular acanthosis [box] with superficial papillary dermal fibrosis [box].

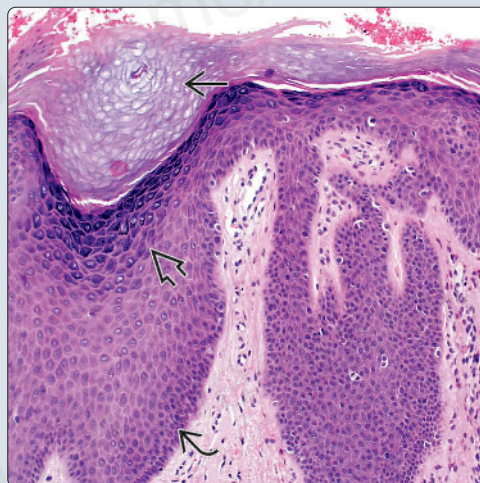


### Irregular Acanthosis With Hypergranulosis

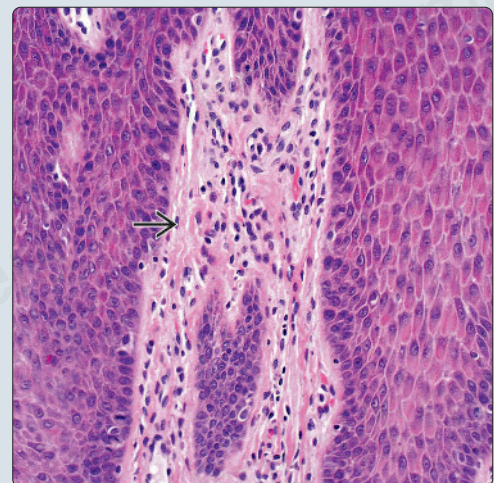


### Irregular Acanthosis

(Left) Typical findings include hyperorthokeratosis [box], hypergranulosis [box], and an irregular acanthosis [box]. (Courtesy S. Billings, MD.) (Right) Vertically oriented papillary dermal fibrosis [box] is a characteristic feature of lichen simplex chronicus. (Courtesy S. Billings, MD.)



### Vertical Orientation of Papillary Dermal Collagen





## TERMINOLOGY

### Abbreviations

- Lichen simplex chronicus (LSC)

### Synonyms

- Circumscribed neurodermatitis
- Localized variants: Lichen nuchae, pruritus vulvae, pruritus scroti, and pruritus ani

### Definitions

- Skin changes caused by chronic itching and scratching

## ETIOLOGY/PATHOGENESIS

### Pruritus

- Underlying trigger for skin scratching
- Number of conditions can cause pruritus: Other medical disorders, other dermatologic disorders, nerve proliferation, psychological disorders
- Main dermatoses causing underlying pruritus: Atopic dermatitis, allergic contact dermatitis, insect bites, and stasis dermatitis

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Not well established
- Age
  - Peak incidence occurs between 30-50 yr
  - Uncommon in children
- Sex
  - Women affected more than men
- Ethnicity
  - No reported differences in frequency among races

### Presentation

- Circumscribed, erythematous, thickened, scaly papules or plaques with lichenification and excoriations
- Affected area often hyperpigmented
- Usually single lesion
- Common sites: Posterior/lateral neck, extensor regions of forearms, thighs, lower legs, ankles, vulva, scrotum, and perianal region

### Laboratory Tests

- If underlying disease is suspected as cause of pruritus
  - Complete blood count with differential analysis, comprehensive blood chemistry profile, thyroid function tests, and chest x-ray helpful

### Treatment

- Options, risks, complications
  - Prevent continued traumatization/aggravation of affected areas, usually through discussion with patient
  - Treat any underlying disorders causing pruritus
- Drugs
  - Topical and intralesional glucocorticoids are mainstay
  - Oral H1 antihistamines
  - Doxepin cream and capsaicin cream sometimes used to decrease pruritus

- Other treatments include phototherapy, photochemotherapy, botulinum toxin injections, and topical immunomodulators
- Topical/oral antibiotics for infected lesions

### Prognosis

- Variable, as there are many causes of LSC, but usually benign

## MICROSCOPIC

### Histologic Features

- Compact hyperorthokeratosis with sometimes focal parakeratosis
- Irregular acanthosis
- Hypergranulosis
- Vertically oriented superficial papillary dermal fibrosis is characteristic feature
- Perivascular inflammatory infiltrate with mild vascular ectasia
- Nerve hyperplasia or hypertrophy can be seen

## DIFFERENTIAL DIAGNOSIS

### Histologic

- Psoriasis
  - Neutrophils often present in stratum corneum
  - Confluent parakeratosis
  - Hypogranulosis
  - Regular acanthosis
  - Edematous papillary dermis with more tortuous vessels
- Chronic spongiotic dermatitis
  - More prominent intercellular edema with lymphocytic infiltrate
- Seborrheic dermatitis
  - More likely to have neutrophils in stratum corneum, specifically at edges of follicular ostia
  - Follicular involvement with mixed inflammatory infiltrate
- Chronic superficial cutaneous fungal infection
  - More likely to have neutrophils in stratum corneum
  - Fungal organisms seen in stratum corneum; may require PAS or GMS stain
- Keratoacanthoma (KA) or squamous cell carcinoma (SCC)
  - KA and SCC have endophytic or invasive architecture and cytologic atypia
  - KA and SCC more likely to have perforating elastic fibers

### Clinical

- Psoriasis
  - Well-demarcated lesions with silvery scale
- Lichen planus
  - Purple, polygonal, planar papules
- Dermatophyte infection
  - Generally annular and accompanied by mild scale

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2. Lotti T et al: Prurigo nodularis and lichen simplex chronicus. *Dermatol Ther.* 21(1):42-6, 2008

## Prurigo Nodularis

## KEY FACTS

## TERMINOLOGY

- Chronic, thickened, and excoriated nodules resulting from chronic skin trauma, usually due to pruritus
- Synonyms
  - Nodular prurigo, picker's nodule

## CLINICAL ISSUES

- Dome-shaped nodules, often with scaly and excoriated surface
- Nodules are often grouped and occur on extensor surfaces of limbs, though they can occur anywhere that can be reached
- Associated pruritus often intermittent
- Lesions range from several millimeters to 2 cm

## MICROSCOPIC

- Cup-shaped acanthosis
- Hyperorthokeratosis
- Hypergranulosis

- Vascular hyperplasia and ectasia
- Mild perivascular inflammatory infiltrate consisting predominantly of lymphocytes

## TOP DIFFERENTIAL DIAGNOSES

- Lichen simplex chronicus
  - Epidermal hyperplasia is not as pronounced
- Keratoacanthomas
  - Exoendophytic crateriform growth pattern
  - Well-differentiated, "glassy" keratinocytes
- Hypertrophic lichen planus
  - Hyperplastic epidermis with wedge-shaped hypergranulosis
- Pseudoepitheliomatous hyperplasia
  - Special stains for microorganisms may help distinguish
- Hypertrophic lupus erythematosus
  - Classic features of lupus will still be present

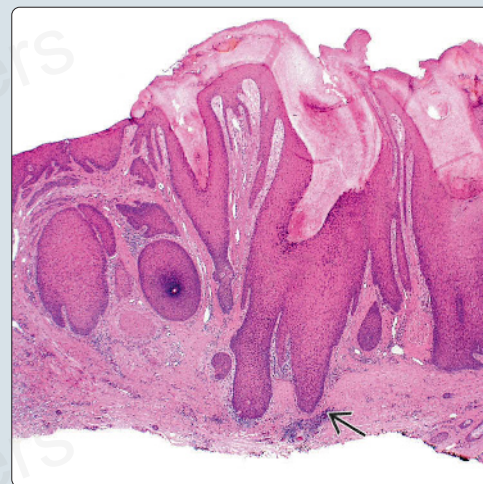
## Excoriated Nodules of Prurigo Nodularis

(Left) Numerous excoriated nodules are present, noticeably within areas of arm's reach, on the legs of this patient with prurigo nodularis. (Courtesy A. Lipworth, MD.)

(Right) Prurigo nodularis shows cup-shaped acanthosis at low power. (Courtesy S. Billings, MD.)



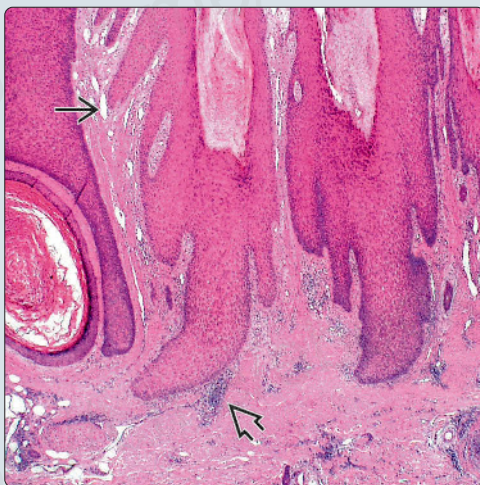
## Cup-Shaped Acanthosis



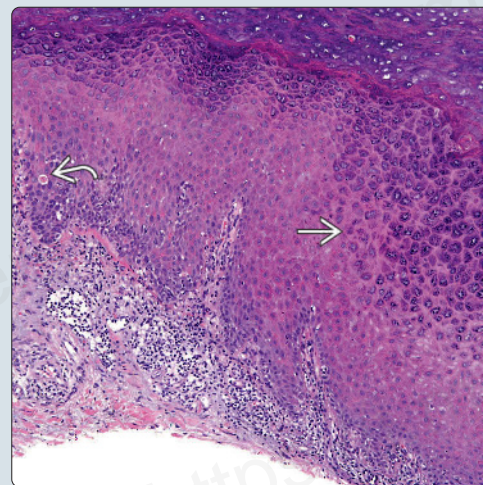
## Dilated Dermal Vessels and Chronic Inflammation

(Left) In addition to dilated dermal vessels, a chronic inflammatory infiltrate is often present along the periphery of the lesion.

(Right) Hypertrophic lichen planus also shows epidermal hyperplasia, but it is usually not as pronounced as in prurigo nodularis, is not as symmetrically cup-shaped, should show interface changes ± dyskeratotic cells, and typically has areas of wedge-shaped hypergranulosis.



## Wedge-Shaped Hypergranulosis of Hypertrophic Lichen Planus



## TERMINOLOGY

### Abbreviations

- Prurigo nodularis (PN)

### Synonyms

- Nodular prurigo, picker's nodule

### Definitions

- Chronic, excoriated, and thickened nodules resulting from chronic trauma to skin, usually due to pruritus

## ETIOLOGY/PATHOGENESIS

### Pruritus

- Underlying trigger for skin scratching
- Number of conditions can cause pruritus: Other medical disorders, other dermatologic disorders, nerve proliferation, psychological disorders

## CLINICAL ISSUES

### Epidemiology

- Age
  - 5-75 years old
  - Individuals with both atopy and PN tend to be younger
- Sex
  - M:F = 1:1

### Presentation

- Dome-shaped nodules, often with scaly and excoriated surface
- Lesions range from several millimeters to 2 cm
- Halo of postinflammatory pigmentation is possible
- Nodules are often grouped and occur on extensor surfaces of limbs, though they can occur anywhere that can be reached
- Palms and soles usually spared
- Associated pruritus often intermittent
- Nodular prurigo eczema occurs when nodular prurigo arises in region of eczema
- Nodules may arise from insect bite

### Laboratory Tests

- If underlying disease is suspected
  - Complete blood count with differential analysis, comprehensive blood chemistry profile, thyroid function tests, and chest x-ray helpful

### Treatment

- Options, risks, complications
  - Prevent continued traumatization/aggravation of affected areas, usually through patient counseling
  - Treat any underlying disorders causing pruritus
- Drugs
  - Topical and intralesional glucocorticoids are mainstay
  - Oral H1 antihistamines
  - Doxepin cream and capsaicin cream sometimes used to decrease pruritus
  - Other treatments include phototherapy, photochemotherapy, botulinum toxin injections, topical immunomodulators, and cryotherapy
  - Topical/oral antibiotics for infected lesions

### Prognosis

- Variable, as there are many causes of PN, but usually benign

## MICROSCOPIC

### Histologic Features

- Cup-shaped acanthosis
- Center of lesion can be ulcerated
- Hyperorthokeratosis
- Hypergranulosis
- Mild epidermal spongiosis is possible
- Subepidermal fibrin deposition is possible
- Mild papillary dermal fibrosis
- Vascular hyperplasia and ectasia
- Mild perivascular inflammatory infiltrate consisting predominantly of lymphocytes
- Nerves may be normal, more numerous, hyperplastic, or sometimes with perineural fibrosis

## DIFFERENTIAL DIAGNOSIS

### Histologic Differential Diagnosis

- **Keratoacanthoma**
  - Central keratotic plug
  - Well-differentiated, "glassy" keratinocytes
  - Neutrophilic microabscesses in epidermis
- **Hypertrophic lichen planus**
  - Hyperplastic epidermis with wedge-shaped hypergranulosis
- **Pseudoepitheliomatous epidermal hyperplasia (PEH)** from number of disorders
  - Special stains for microorganisms may distinguish PEH from PN
  - Usually more dermal inflammation and typically mixed dermal infiltrate
    - Abundant neutrophils, microabscesses, eosinophils, or plasma cells are clue
- **Lichen simplex chronicus**
  - Lichen simplex chronicus patch and plaques tend to be less symmetrical and well demarcated
  - Epidermal hyperplasia is not as pronounced
- **Hypertrophic lupus erythematosus**
  - Extremely rare entity
  - Classic features of lupus will still be present
  - Pseudoepitheliomatous hyperplasia engulfing elastotic material
    - Histologically resemble keratoacanthomas
  - Important to differentiate, as squamous cell carcinomas can arise from longstanding hypertrophic lupus erythematosus lesions

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4. Weigelt N et al: Prurigo nodularis: systematic analysis of 58 histological criteria in 136 patients. *J Cutan Pathol.* 37(5):578-86, 2010



## Frictional Keratosis

## KEY FACTS

## TERMINOLOGY

- Reactive, benign frictional keratosis
- Important to distinguish from leukoplakia, which may be premalignant
- Analogous to lichen simplex chronicus of oral mucosa

## ETIOLOGY/PATHOGENESIS

- Occurs secondary to chronic friction
- Most often seen near biting surfaces of teeth

## CLINICAL ISSUES

- Poorly demarcated, white papules or plaques
- Ulceration, induration, and sharp demarcation should raise suspicion for malignancy or premalignant condition

## MICROSCOPIC

- Benign epithelial hyperplasia
- Papillomatosis
- Surface may be ragged with bacterial colonies

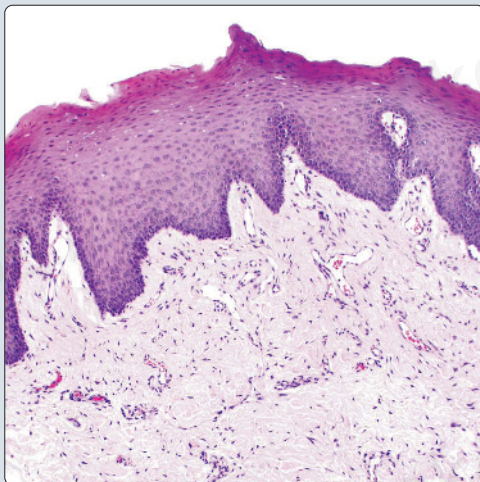
- Hypergranulosis
- Pallor or ballooning of superficial keratinocytes
- No crowding or hyperplasia of basilar keratinocytes
- No cytological atypia

## TOP DIFFERENTIAL DIAGNOSES

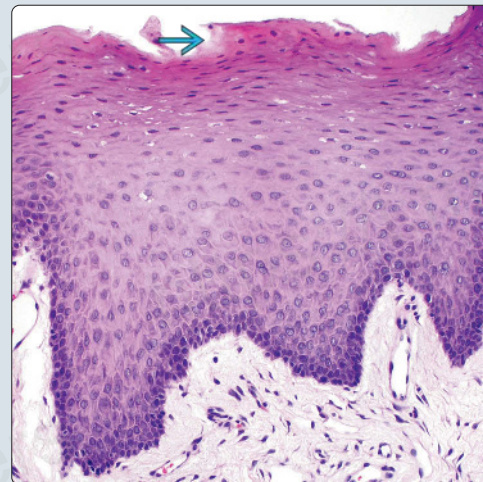
- Leukoplakia
- Hairy tongue
- Human papillomavirus-associated dysplasia
- Squamous cell carcinoma in situ
- Invasive squamous cell carcinoma

## Irregular Acanthosis

(Left) The mucosal epithelium is thickened with irregular elongation of epithelial rete. In the submucosa, there is sparse inflammation along with dilated vessels. (Right) There is acanthosis and hyperkeratosis of the mucosal epithelium. Rete are elongated in an irregular fashion. The basal layer lacks cytological atypia.

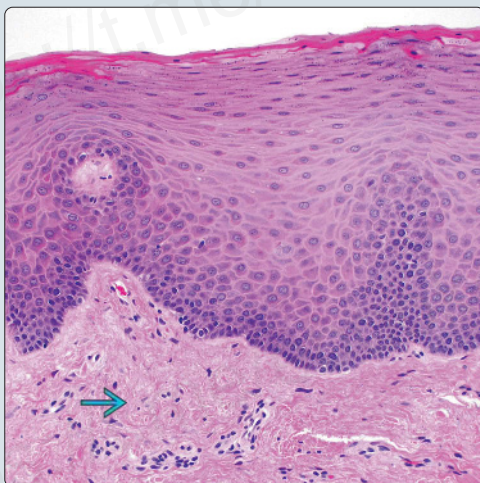


## Acanthotic Mucosal Epithelium

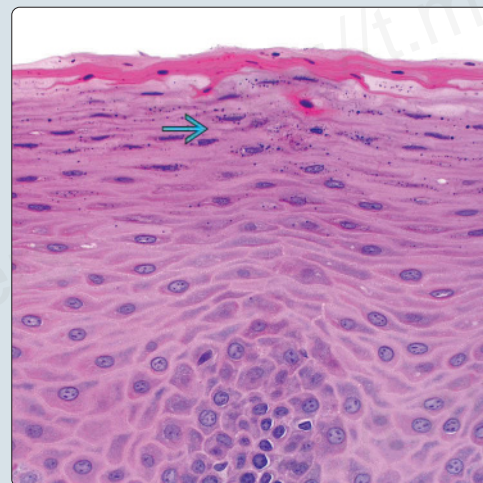


## Submucosal Fibroplasia

(Left) Fibroplasia of the submucosal lamina propria may be posttraumatic but can rarely be an early sign of dysplasia, even if the overlying epithelium lacks architectural or cytological features of dysplasia. (Right) Squamous epithelial cells of the nonkeratinizing mucosal epithelium may acquire keratohyaline granules and undergo keratinization in frictional keratosis.



## Abnormal Keratinization of Epithelium



**TERMINOLOGY****Synonyms**

- Oral lichen simplex chronicus, morsicatio mucosae oris, and leukokeratosis oris

**Definitions**

- Reactive benign hyperplasia of oral mucosal epithelium secondary to chronic frictional forces

**CLINICAL ISSUES****Epidemiology**

- Occurs secondary to chronic frictional forces
  - Biting or chewing lip
  - Poorly fitting dental appliances
  - Raking of teeth against lips
- Most patients are not aware of chronic friction

**Site**

- Most commonly seen near biting surfaces of teeth
  - Buccal mucosa
  - Lateral ventral tongue
  - Lower lip
  - Rare on upper lip

**Presentation**

- Presents as poorly demarcated white papules and plaques
- May have shaggy appearance
- More severe friction may lead to erythema, erosion, or ulceration

**Treatment**

- Options, risks, complications
  - Resolves with removal of frictional forces

**Prognosis**

- Important to monitor
- If no clinical resolution, consider repeat biopsy to exclude dysplasia

**MICROSCOPIC****Histologic Features**

- Epithelial hyperplasia
- Papillomatosis
- Tapering of rete ridges
- May see superficial fissures or clefts
  - Clefts often colonized by bacteria
- Keratinocyte pallor or ballooning
- Mild parakeratosis
- Sparse inflammatory infiltrates in lamina propria

**DIFFERENTIAL DIAGNOSIS****Leukoedema**

- Fine, lacy, white lines on buccal mucosa that are eliminated when mucosa is stretched
- Usually caused by mild irritant (such as cigarette smoke)
- Edema of superficial keratinocytes leads to pallor and ballooning

**Alveolar Ridge Keratosis**

- White, poorly demarcated papules or plaques on keratinizing epithelium
- Common at site of tooth extraction
- Hyperkeratosis and hypergranulosis
  - Resembles lichen simplex chronicus

**Leukoplakia**

- Vague clinical term to denote white keratotic lesions on mucosal epithelium
- Includes premalignant or dysplastic conditions as well as nonspecific lesions
  - Nonspecific lesions sometimes described as hyperkeratosis and acanthosis

**Human Papillomavirus-Associated Dysplasia**

- Sharply demarcated, white papules or plaques
- Papillomatosis
- Hyperkeratosis
- Hypergranulosis
- Koilocytosis
- Apoptotic bodies
- Mitoses in suprabasilar location
- May stain diffusely with p16

**Squamous Cell Carcinoma**

- Cytologically atypical keratinocytes present through full thickness of epithelium (carcinoma in situ), possibly with extension into submucosa (invasive carcinoma)

**Hairy Tongue**

- Hyperplastic papillae colonized by bacteria

**DIAGNOSTIC CHECKLIST****Clinically Relevant Pathologic Features**

- Poorly demarcated, white papules or plaques
- Occur at sites of friction

**Pathologic Interpretation Pearls**

- Benign epithelial hyperplasia
- Hyperkeratosis
  - Ragged clefts in superficial aspect of epithelium with bacterial colonies
- Tapering of rete
- Hypergranulosis
- Lacks crowding of keratinocyte and cytological atypia

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# Psoriasis

## KEY FACTS

### TERMINOLOGY

- Synonym: Psoriasis vulgaris

### CLINICAL ISSUES

- Incidence
  - 1-3% of population affected
- Age
  - Mean at presentation: 25-35 years
- Presentation
  - Sharply demarcated erythematous plaques and patches
  - Overlying silvery white scale
  - Auspitz sign: Pinpoint bleeding occurs when scale is removed
- Site
  - Extensor surfaces of extremities, scalp, trunk, nails, and buttocks

### MICROSCOPIC

- Epidermis

- Confluent parakeratosis
- Regular psoriasiform hyperplasia with thinning over dermal papillae
- Neutrophils migrating through epidermis over dermal papillae
- Neutrophil collections in corneal (Munro microabscesses) and spinous (spongiform pustules of Kogoj) layers
- Dermis
  - Dilated vessels in papillary dermis
  - $\pm$  RBC extravasation
  - Denser perivascular activated lymphocytes, Langerhans cells, and neutrophils

### TOP DIFFERENTIAL DIAGNOSES

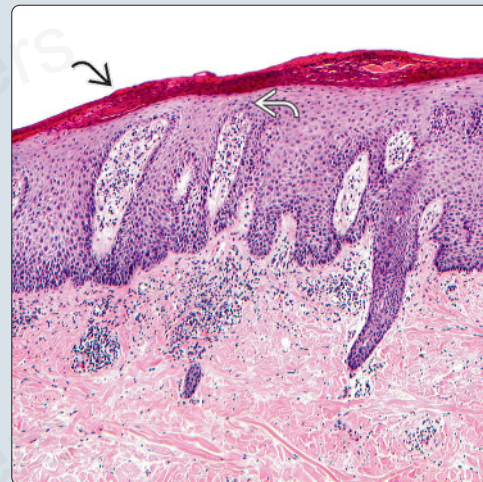
- Chronic eczematous dermatitis
- Lichen simplex chronicus
- Superficial fungal infection
- Pityriasis rubra pilaris

Silvery Thick Scale of Psoriasis

(Left) Psoriasis presents here as an ostraceous, silvery-white, adherent, thick scale over the knuckles on erythematous plaques in the usual extensor location. (Right) In this psoriasis vulgaris plaque, regular psoriasiform hyperplasia is evident with thinning of the suprapapillary plates, confluent parakeratosis with neutrophils, and superficial perivascular lymphocytes. Also note the hypogranulosis.

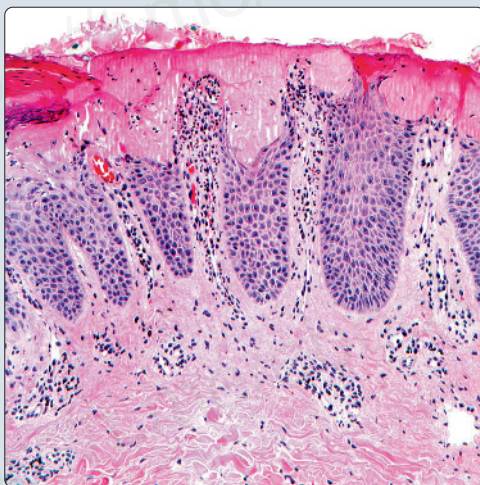


Psoriasiform Hyperplasia and Thinning of Suprapapillary Plates

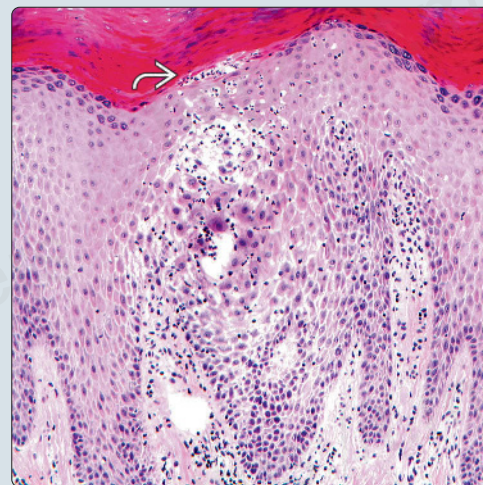


Histopathology of Auspitz Sign

(Left) When the overlying scale is removed, pinpoint bleeding may occur (Auspitz sign). In this image, pulling off the scale has also torn away the suprapapillary epidermal layers causing disruption of the underlying superficial blood vessels. (Right) In established psoriatic plaques, neutrophils can be seen emigrating from the superficial vessels through the overlying epidermis and into the parakeratosis. A Munro microabscess is present.



Intraepidermal Neutrophils in Psoriasis





## TERMINOLOGY

### Synonyms

- Psoriasis vulgaris

### Definitions

- Prototype of psoriasiform dermatoses

## ETIOLOGY/PATHOGENESIS

### Environmental/Lifestyle Associations

- Stress
- Comorbidities of metabolic syndrome
  - Obesity, hypertension, diabetes mellitus, dyslipidemia, cardiovascular disease
- Some organisms
  - Viruses: Human papillomavirus (HPV)5, HPV36, and HIV
  - Bacteria: *Streptococcus pyogenes*, *Staphylococcus aureus*
  - Fungi: *Malassezia* spp, *Candida albicans*
- Trauma
  - Koebner reaction: Present in 1/3 of cases
- Medications
  - Particularly  $\beta$ -blockers, ACE-inhibitors, clonidine, nonsteroidal antiinflammatory drugs, antimalarials, and some  $\beta$ -lactam antibiotics

### Genetic

- Extremely complicated and ever evolving
- Polygenic, but more common in monozygotic than dizygotic twins

### Immunological

- Very complex; detailed explanation is beyond scope of chapter
- T cells are recruited to superficial dermal vessels
  - CD4(+) T cells mostly remain in dermis
  - CD8(+) T cells infiltrate epidermis
- Dermal dendritic cells exacerbate CD4 T-cell recruitment and cytokine cascade
  - Plasmacytoid dendritic cells produce IFN- $\alpha$
  - Langerhans cells stimulate IL-22 producing T cells
  - Myeloid dendritic cells produce TNF- $\alpha$ , produce and stimulate multiple cytokines, stimulate T cells, and increase IFN- $\gamma$
- Increase in cytokines causes keratinocyte proliferation and epidermal hyperplasia

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - 1-3% of population affected
- Age
  - Mean at presentation: 25-35 years
  - Type 1 psoriasis
    - Presents by age 40
  - Type 2 psoriasis
    - Presents in 5th-6th decades
- Sex
  - In children
    - More common in girls
  - In adults

- No male/female predilection

- Ethnicity
  - Occurs in all ethnicities

### Presentation

- Sharply demarcated erythematous plaques and patches
  - Overlying silvery white scale
    - Auspitz sign: Pinpoint bleeding occurs when scale is removed
- Pruritus is common
- Predilection for extensor surfaces of extremities (elbows and knees), scalp, trunk, nails, and buttocks
  - Rarely involves face, lips, and oral mucosa
- Patients may develop seronegative polyarthritis
- Woronoff ring: White annular ring around erythematous plaques undergoing phototherapy or topical treatment

### Treatment

- Drugs
  - Topical
    - Emollients, coal tar, retinoids, corticosteroids, vitamin D analogues, calcineurin inhibitors, etc.
  - Phototherapy
    - Psoralen plus ultraviolet A, ultraviolet B, excimer laser, etc.
  - Systemic
    - Methotrexate, cyclosporine, retinoids, etc.
  - Biologics
    - Etanercept, infliximab, adalimumab, efalizumab, ustekinumab, etc.

### Prognosis

- Typically chronic course with periods of relapse and remission
  - Depends on psoriasis variant and type of treatment employed

### Variants

- **Guttate psoriasis**
  - Characterized by acute onset of numerous drop-like, 1-10 mm in diameter, salmon-pink papules with overlying scale
    - Latin word gutta means drop
    - Primarily trunk and extremities
  - Often preceded by *S. pyogenes* infection
  - Affects individuals under 30 years of age
  - Typically resolves, but higher risk of plaque psoriasis later on
- **Small plaque psoriasis**
  - Papules and plaques up to 3 cm in diameter
  - Plaques may be more randomly distributed over body
  - Unlike guttate psoriasis, chronic process
- **Pustular psoriasis**
  - Individual &/or confluent yellow-white pustules
    - Underlying skin may appear erythematous &/or edematous
  - May be generalized (von Zumbusch psoriasis) with fever &/or malaise, localized, annular, or seen only during pregnancy
- **Palmoplantar pustulosis (pustulosis palmaris et plantaris)**

- Hyperkeratosis with clusters of sterile pustules on ventral hands &/or feet
- **Acrodermatitis continua of Hallopeau**
  - Painful eruption of sterile pustules with erythematous base on 1 or more digits
    - With onychodystrophy, anonychia, &/or osteolysis
- **Erythrodermic psoriasis**
  - Characterized by psoriatic plaques involving  $\geq 90\%$  of body surface
  - Thin or flat plaques on warm, erythematous skin
  - Fine, flaky scale; not coarse as in psoriasis vulgaris
  - Increased morbidity from fluid and electrolyte derangements, protein loss, high-output heart failure, or superimposed infection
- **Inverse psoriasis**
  - Localized to intertriginous regions
  - Shiny lesions without typical scale
- **Scalp psoriasis**
  - Localized to scalp
- **Sebopsoriasis**
  - Psoriatic plaques in seborrheic distribution
- **Nail psoriasis**
  - Nail matrix and nail plate involvement
    - Nail pitting, salmon patch, or oil drop sign
    - Leukonychia, silvery subungual hyperkeratosis
  - Separation of nail plate and nail bed
    - Onycholysis
  - Nail bed involvement
    - Red spots in lunula, nail bed hemorrhages
- **Reiter disease**
  - Combination of
    - Conjunctivitis
    - Urethritis
    - Arthritis
    - Psoriasiform skin lesions: Annular circinate balanitis, keratoderma blennorrhagicum, or nail dystrophy

## MICROSCOPIC

### Histologic Features

- **In early lesions**
  - **Epidermis**
    - Parakeratosis may not be confluent (parakeratotic mounds)
    - Lesser degree of psoriasiform hyperplasia
    - Neutrophils migrating through epidermis over dermal papillae
    - Neutrophil collections in corneal layer (Munro microabscesses)
    - $\pm$  increased mitoses in basal layer
    - $\pm$  spongiosis
  - **Dermis**
    - Dilated vessels in papillary dermis
    - $\pm$  RBC extravasation
    - Mild perivascular lymphocytic infiltrate with Langerhans cells and rare neutrophils
- **In established lesions**
  - **Epidermis**
    - Confluent parakeratosis

- Regular psoriasiform hyperplasia with thinning over dermal papillae
- Neutrophils migrating through epidermis over dermal papillae
- Neutrophil collections in corneal and spinous (spongiform pustules of Kogoj) layers
- Increased mitoses in basal layer
- $\pm$  spongiosis
- **Dermis**
  - Dilated vessels in papillary dermis
  - $\pm$  RBC extravasation
  - Denser perivascular activated lymphocytes, Langerhans cells, and neutrophils
- **In treated lesions**
  - Epidermis slowly returns to normal skin
    - Loss of parakeratosis, return of stratum granulosum, decrease of acanthosis, and loss of suprapapillary thinning
  - However, dermal changes of capillary dilatation, mild acanthosis, and mild inflammatory infiltrate tend to persist
    - Even up to 1 year after treatment in some patients

## ANCILLARY TESTS

### Histochemistry

- AFB, GMS, or PAS to rule out fungal or bacterial infection

## DIFFERENTIAL DIAGNOSIS

### Histologic

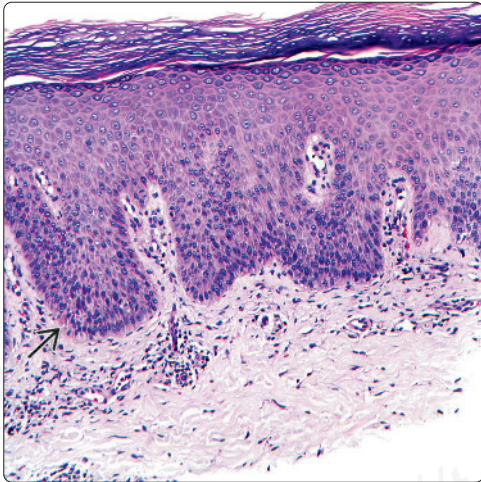
- **Chronic eczematous dermatitis**
  - Generally more prominent spongiosis
  - Does not tend to have parakeratotic mounds or Munro microabscesses
  - Dermal eosinophils
  - Psoriasiform hyperplasia is typically more irregular
- **Superficial fungal infection**
  - Presence of fungus or dermatophytes can be eliminated with negative GMS or PAS stains
- **Lichen simplex chronicus**
  - Irregular acanthosis, wedge-shaped hypergranulosis
  - Munro microabscesses are less frequent
  - Superficial dermal fibrosis is common
- **Pityriasis rubra pilaris**
  - May have alternating parakeratosis and orthokeratosis in checkerboard pattern
  - Parakeratosis "shouldering" of hair follicles
  - Follicular keratin plugs are common

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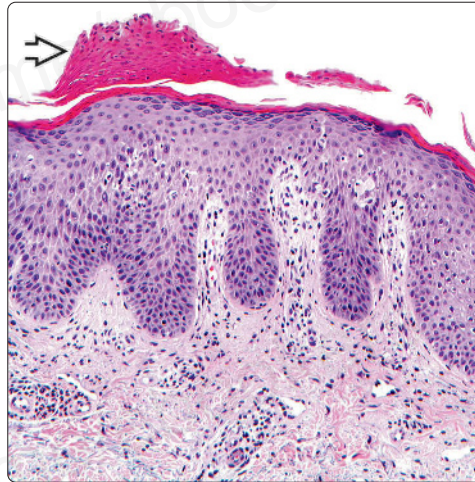
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**Early Psoriasis With Mild Psoriasiform Hyperplasia**



**Guttate Psoriasis With Parakeratotic Mounds**

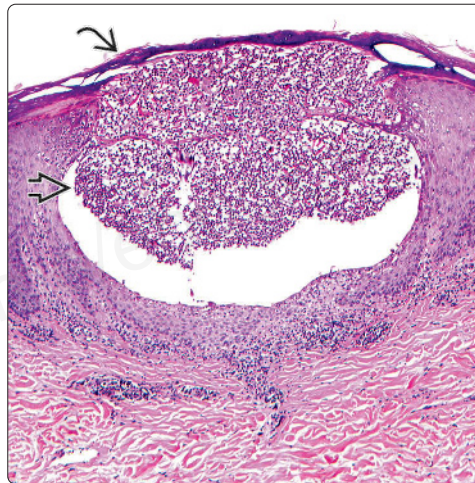


(Left) In early lesions of psoriasis, psoriasiform hyperplasia [1] may be mild. The underlying superficial perivascular infiltrate is sparse and consists of predominantly lymphocytes. The overlying corneal layer still has "basket weave" keratin, indicating recent onset. (Right) In guttate psoriasis, in addition to the other typical features of psoriasis, occasional parakeratotic mounds [2] may be seen in the corneal layer with confluent parakeratosis in between them. Early lesions of psoriasis may appear similar.

**Thick Yellow Scale of Pustular Psoriasis**

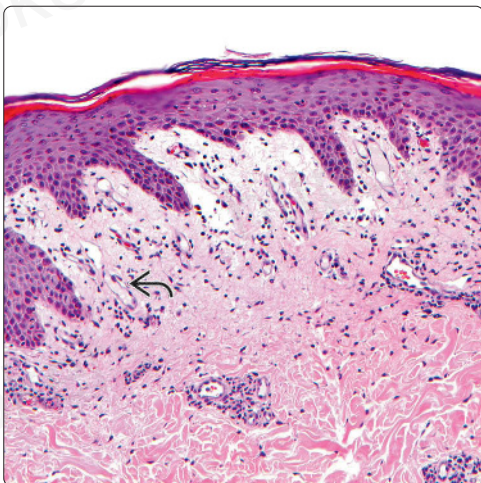


**Intraepidermal Pustule in Pustular Psoriasis**

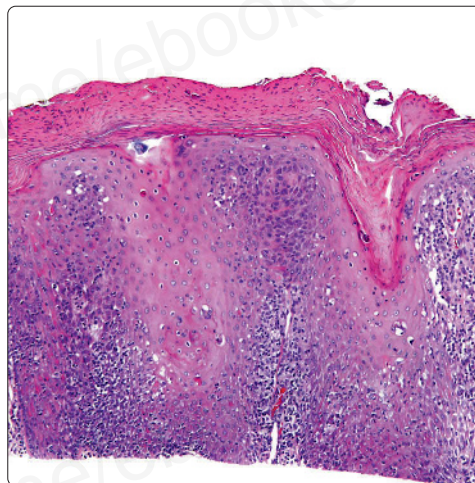


(Left) In this photograph of pustular psoriasis, a thick yellow-brown scale covers an erythematous patch. (Right) In this example of pustular psoriasis, there is a large intraepidermal sterile pustule [1] covered by a thin layer of scale [2].

**Dermal Edema in Erythrodermic Psoriasis**



**Spongiotic Dermatitis With Psoriasiform Features**



(Left) Erythrodermic psoriasis is defined by  $\geq 90\%$  of body surface involvement by confluent plaques. Dilation of superficial vessels [1] and papillary dermal edema are more prominent. (Right) Spongiotic (eczematous) dermatides can at times also be psoriasiform as in this image. However, there is typically more spongiosis, parakeratosis without neutrophils, and it usually lacks dilated superficial vessels. There is also typically serum in the stratum corneum (giving it a wet appearance).



## KEY FACTS

### TERMINOLOGY

- Idiopathic lymphoplasmacellular mucositis-dermatitis is generic term for any inflammatory accumulation of plasma cells at mucosal or cutaneous sites
- Zoon balanitis is reserved for localized involvement of prepuce or glans penis

### CLINICAL ISSUES

- Benign process with chronic course, with only few cases that respond to corticosteroids
- In men, most cases are cured by circumcision
- Laser ablation can also be effective

### MACROSCOPIC

- Red plaque, usually well demarcated
- Erythematous, moist and shiny
- Usually is single lesion, but it may consist of several confluent macules

### MICROSCOPIC

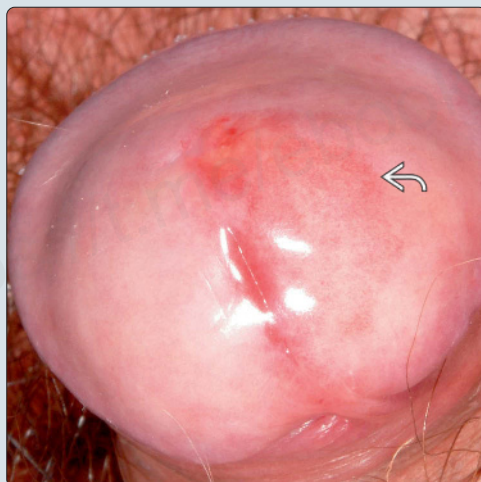
- Epithelium appears thinned and flattened
  - Sometimes may be partially detached or even absent
- Mild spongiosis
- Dense lymphocytic lichenoid infiltrate in upper and mid submucosa, with abundant mature plasma cells
- Epithelium with diamond- or lozenge-shaped, flattened keratinocytes

### TOP DIFFERENTIAL DIAGNOSES

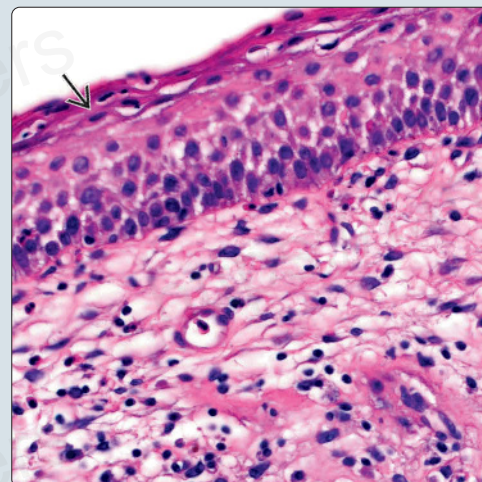
- Primary and secondary syphilis
  - Contains more lymphocytes and neutrophils
  - Primary syphilis is usually ulcerated
  - Secondary syphilis shows psoriasiform hyperplasia
- Cutaneous plasmacytosis
  - Infiltrate is more dense and homogeneous and appears at cutaneous, not mucosal, sites

**Erythematous Well-Demarcated Plaque**

(Left) Zoon balanitis presents as an erythematous plaque that is often well demarcated. (Right) This case of Zoon balanitis demonstrates an epithelium with diamond-shaped, flattened keratinocytes, mild spongiosis, and submucosal inflammation.

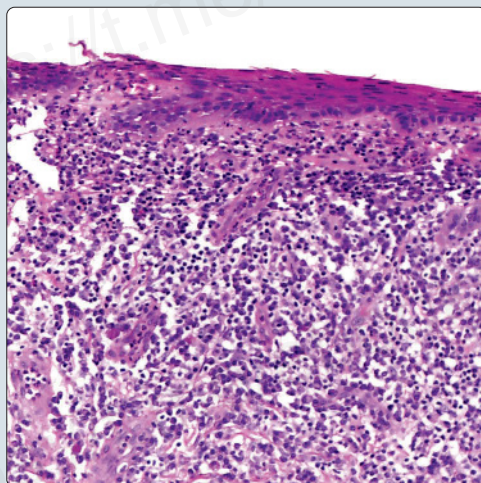


**Atrophic Epithelium With Flattened Keratinocytes**

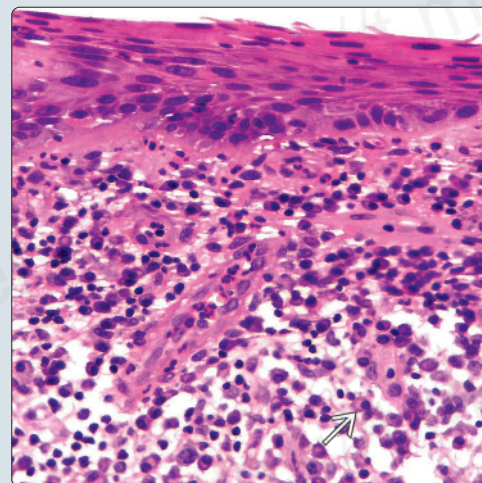


**Dense Lichenoid Infiltrate of Plasma Cells**

(Left) Another example of Zoon balanitis demonstrates a dense lichenoid inflammatory infiltrate mainly composed of plasma cells. (Right) High-power view of Zoon balanitis shows numerous submucosal plasma cells with characteristic eccentric nuclei.



**Numerous Submucosal Plasma Cells**



## TERMINOLOGY

### Synonyms

- Plasmacytosis mucosae
- Plasma cell balanitis
- Balanitis circumscripta plasmacellularis (men)
- Vulvitis circumscripta plasmacellularis (women)
- Plasma cell cheilitis (lip)
- Plasmocytosis circumorificialis (oral)
- Idiopathic lymphoplasmacellular mucositis-dermatitis (skin and mucosal surfaces)

### Definitions

- Idiopathic lymphoplasmacellular mucositis-dermatitis is generic term for any inflammatory accumulation of plasma cells at mucosal or cutaneous sites
- Zoon balanitis is reserved for localized involvement of prepuce or glans penis

## ETIOLOGY/PATHOGENESIS

### Unknown

- Poor penile hygiene or chronic irritation from warmth or rubbing has been suggested
- Does not occur in circumcised men

## CLINICAL ISSUES

### Epidemiology

- Age
  - Any age, but usually from 3rd decade onward in uncircumcised men
- Sex
  - Predominantly affects men
  - Cases in women have been questioned by some authors

### Presentation

- Erythematous plaques
  - Sometimes asymptomatic or give rise to pruritus or dysuria
- No inguinal adenopathy
- Women
  - Vulva shows lesions similar to those in men
  - Asymptomatic or produces dyspareunia, dysuria, pruritus, or pain
- Oral mucous, lips, cheeks, or tongue
  - Called plasmacytosis circumorificialis
  - Commonly confused with carcinoma

### Treatment

- Only few cases respond to corticosteroids
  - In men, most cases are cured by circumcision
  - Laser ablation can also be effective

### Prognosis

- Benign process with chronic course

## MACROSCOPIC

### General Features

- Red plaque, usually well demarcated
- Erythematous, moist and shiny

### Size

- Usually is single lesion, but it may consist of several confluent macules

## MICROSCOPIC

### Histologic Features

- Dense lichenoid infiltrate in upper and mid submucosa or dermis
- Lymphocytic infiltrate with abundant mature plasma cells
- Superficial vascular proliferation
- Some extravasated erythrocytes and hemosiderin deposits
- Some mast cells, eosinophils, and neutrophils
- Mucosa or epidermis
  - Appears thinned and flattened, with mild spongiosis
  - Sometimes may be partially detached or even absent

### Cytologic Features

- Mucosa or epidermis is composed of diamond- or lozenge-shaped, flattened keratinocytes
- No cytologic atypia

## ANCILLARY TESTS

### Immunohistochemistry

- Kappa:lambda ratio approximately 2:1

## DIFFERENTIAL DIAGNOSIS

### Primary and Secondary Syphilis

- Contains more lymphocytes and neutrophils
- Primary syphilis is usually ulcerated
  - In Zoon balanitis, ulceration is uncommon
- Spirochetes may be visualized with silver stains
- Secondary syphilis shows psoriasiform hyperplasia
  - In Zoon balanitis, mucosa is thinned

### Cutaneous Plasmacytosis

- Infiltrate is more dense and homogeneous and appears at cutaneous, not mucosal, sites
- Serum electrophoresis shows monoclonal peak

### Cutaneous Malignancy (Squamous Cell Carcinoma In Situ or Extramammary Paget Disease)

- Epithelial atypia is not seen in Zoon balanitis
- More of a clinical differential diagnosis

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Dense lichenoid infiltrate in upper and mid submucosa or dermis with numerous plasma cells
- Mucosa or epidermis appears thinned and flattened, with mild spongiosis

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## KEY FACTS

### CLINICAL ISSUES

- Classic triad: Arthritis, urethritis, conjunctivitis
- Cutaneous manifestations on soles (keratoderma blennorrhagicum), extensor surfaces of legs, penis (balanitis circinata), dorsal hands/fingers, nails, scalp
- Ocular manifestations include: Bilateral mucopurulent conjunctivitis, iritis, iridocyclitis, uveitis with glaucoma, keratitis, blindness
- GU manifestations include: Urethritis, prostatitis, seminal vesiculitis, hemorrhagic cystitis, cervicitis, salpingitis
- *Chlamydia trachomatis* causes majority of urethritis; may trigger entire syndrome

### MICROSCOPIC

- Acanthosis with elongation and hypertrophy of epidermal rete ridges, thin suprapapillary plates, and overlying parakeratosis
- Neutrophilic dermatitis with spongiform pustules and microabscesses

- Perivascular lymphohistiocytic infiltrate and neutrophils in upper dermis

### TOP DIFFERENTIAL DIAGNOSES

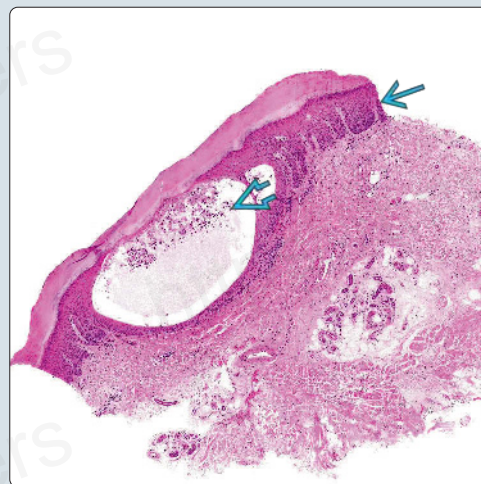
- Pustular psoriasis
  - Indistinguishable histologically, can have associated arthritis
  - Lacks ocular and GU symptoms
- IgA pemphigus
  - Positive DIF
- Dermatitis herpetiformis
  - Positive DIF, positive antitissue transglutaminase, antiendomysial, and antigliadin antibodies

Pink Scaly Papules Coalescing Into Plaques

(Left) *Keratoderma blennorrhagicum* (KB) presents as pink, scaly to crusted papules coalescing into plaques on the soles of the feet. (Courtesy A. Dominguez, MD.) (Right) A lesion of KB shows acral skin with psoriasiform acanthosis and formation of an intraepidermal pustule with abundant neutrophils.



Acral Skin With Intraepidermal Pustule Formation

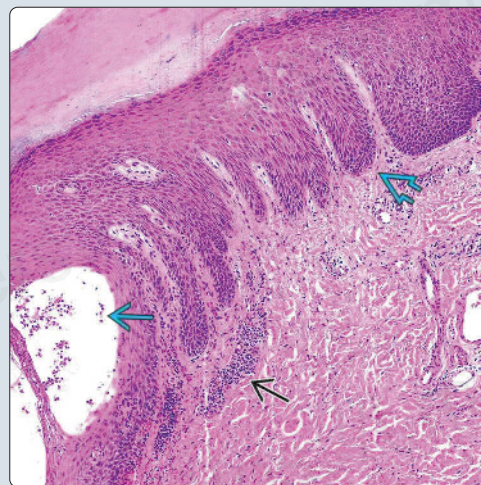


Intraepidermal Pustule Formation

(Left) On biopsy, KB shows an intraepidermal collection of neutrophils with pustule formation. Acanthosis with blunted rete pegs is also seen, along with a mild dermal lymphocytic infiltrate. (Right) At higher magnification, KB shows intraepidermal neutrophilic collections, regular epidermal acanthosis, and perivascular lymphocytic infiltrate in the superficial papillary dermis.



Regular Acanthosis and Neutrophils





## TERMINOLOGY

### Definitions

- Classic triad of arthritis, urethritis, conjunctivitis
  - Can occur together or in sequence, often following urethral or enteric infection
- Skin manifestations are similar to psoriasis
  - Erythematous, hyperkeratotic macules and plaques on palms, soles, trunk, and extremities
  - Acral hyperkeratosis with pustules may develop (keratoderma blennorrhagicum)
  - Superficial erosions on glans penis (circinate balanitis)

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- Often follows nonspecific urethritis or enteric infections
  - *Chlamydia trachomatis* is most common preceding infection
  - *Chlamydia pneumoniae*
  - Bacillary or amebic dysentery
    - *Shigella*
    - *Salmonella*
    - *Yersinia*
    - *Campylobacter*
  - Other causes
    - *Mycoplasma* species
    - *Streptococcus viridans*
    - *Clostridium difficile*
    - *Cryptosporidium* species
    - Hepatitis B immunization
    - IFN- $\alpha$  treatment
    - HIV

### Strongly Associated With HLA B27 Genotype and Ankylosing Spondylitis

- 90% of Reiter syndrome patients are positive
- HLA-B51 also reported
- New research is targeting role of gut microbiome as it relates to and affects ankylosing spondylitis and reactive arthritis

## CLINICAL ISSUES

### Epidemiology

- Age
  - Young men (20-30 years)
- Sex
  - M:F = 10:1
  - May be underdiagnosed in women

### Presentation

- Classic triad
  - Arthritis, urethritis, conjunctivitis
    - Mnemonic: "Can't see, can't pee, can't climb tree"
- Genitourinary
  - Urethritis, prostatitis, seminal vesiculitis, hemorrhagic cystitis, cervicitis, salpingitis
  - Vulvitis can occur in affected women
  - *C. trachomatis* causes majority of urethritis; may trigger entire syndrome

- Ocular
  - Bilateral mucopurulent conjunctivitis
  - Iritis, iridocyclitis
  - Uveitis with glaucoma
  - Keratitis
  - Blindness
- Musculoskeletal
  - Polyarthritis of large, weight-bearing joints
  - Ankylosing spondylitis
  - Osteoporosis, periostitis, systemic amyloidosis
- Cutaneous
  - Soles (keratoderma blennorrhagicum), extensor surfaces of legs, penis (balanitis circinata), dorsal hands/fingers, nails, scalp
  - Salmon pink to red hyperkeratotic (cobblestone appearance) macules, papules, and plaques with erythematous halos on palms, soles, trunk, and extremities
  - Keratoderma blennorrhagicum (KB)
    - Pustules on palms and soles
  - Mucosal erosions and ulcerations (genital and oral)
  - Stomatitis, psoriasis-like nail changes (pitting, oil spots)
  - Folliculitis, vasculitis, and erythema nodosum-like features herald systemic disease
- Cardiovascular
  - Aortic valve insufficiency, AV nodal block

### Treatment

- Drugs
  - Antibiotics for underlying infection, if still present
    - Dual therapy with rifampin and doxycycline has proven better at eliminating chlamydial infections than monotherapy
- Symptomatic treatment
  - Most patients respond well to NSAIDs
  - TNF blockers are efficacious in many refractory reactive arthritides

### Prognosis

- Can resolve spontaneously
- Most commonly joint pain, ankylosing spondylitis, and back pain persist chronically
- Relapsing and remitting course is less common
- Serious complications include blindness, sterility
- HIV-infected patients can have severe disease
- Risk of death increases with aortic insufficiency, systemic amyloidosis, AV nodal involvement, severe weight loss

## MACROSCOPIC

### General Features

- Resembles psoriasis
  - Pink to red scaly macules, papules, and plaques on trunk, extremities, hands, and feet
- Pustules may present on palms and soles
- Mucosal ulcerations and erosions

**MICROSCOPIC****Histologic Features**

- Acanthosis with elongation and hypertrophy of epidermal rete ridges, thin suprapapillary plates, and overlying parakeratosis
- Neutrophilic dermatitis with spongiform pustules and microabscesses
- Perivascular lymphohistiocytic infiltrate and neutrophils in upper dermis
- Evidence of sterile folliculitis with perifollicular vasculopathy may be found in widespread systemic disease

**ANCILLARY TESTS****Histochemistry**

- PAS and silver stains to rule out fungal infection

**Microbiology Work-Up of Associated GU/GI Infection**

- Culture
  - Susceptibilities indicated if cultures performed
- PCR
- Serology

**Testing for Other STI/STDs If Warranted**

- HIV, syphilis, etc.

**DIFFERENTIAL DIAGNOSIS****Pustular Psoriasis**

- Indistinguishable histologically, can have associated arthritis
- Lacks ocular and GU symptoms

**IgA Pemphigus**

- Can be histologically indistinguishable
- Positive DIF

**Dermatitis Herpetiformis**

- Positive DIF, positive antitissue transglutaminase, antiendomysial, and antigliadin antibodies
- Clinically, lesions are intensely pruritic
- All symptoms resolve with gluten-free diet

**Psoriasis**

- Can present with joint pain
- No ocular and GU symptoms, no associated GU or GI infection

**Psoriatic Arthritis**

- No associated GU or GI infection, no conjunctivitis

**DIAGNOSTIC CHECKLIST****Clinically Relevant Pathologic Features**

- Classic triad of arthritis, urethritis, conjunctivitis
- Pink to red psoriasiform plaques on hands, feet, trunk, and extremities, pustules on palms and soles (KB), mucosal erosions and ulcerations
- Various cardiovascular, musculoskeletal, ophthalmologic, and GU symptoms
- Arthritis is most common relapsing symptom

**Pathologic Interpretation Pearls**

- Histologically indistinguishable from pustular psoriasis

- Psoriasiform hyperplasia
- Neutrophilic dermatitis with spongiform pustules and microabscesses
- Diagnosis is dependent on clinicopathologic correlation

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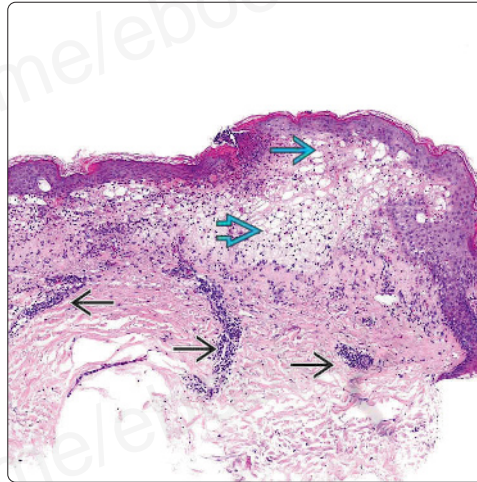
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**Intraepidermal Pustular Bulla**

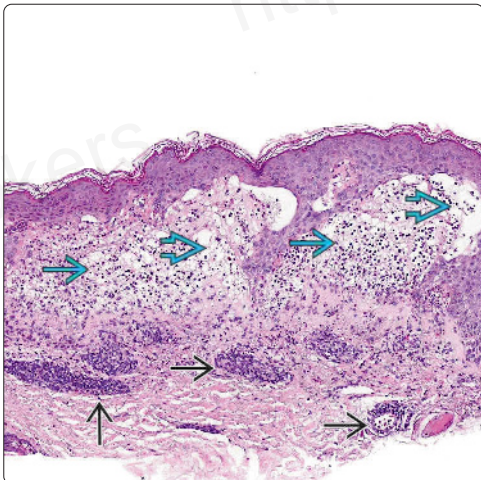


**Acute Neutrophilic Spongiosis**

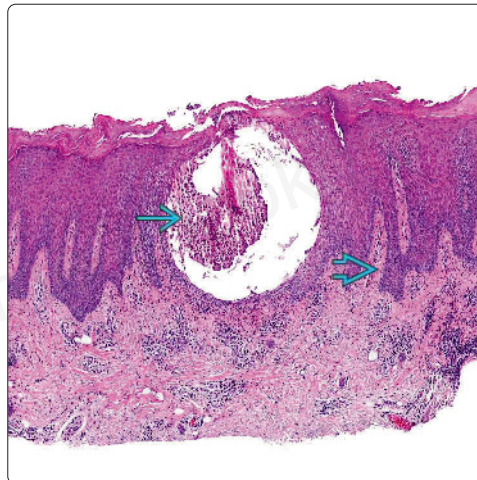


(Left) A medium-magnification image demonstrates a neutrophilic dermatosis with intraepidermal bulla formation associated with a mixed inflammatory infiltrate in a biopsy from a patient with reactive arthritis. (Right) Another biopsy from a patient with reactive arthritis shows an acute spongiotic dermatitis with neutrophils in the epidermis, with marked spongiosis and intraepidermal pustule formation. A superficial, predominantly lymphocytic, perivascular infiltrate is present in the dermis.

**Neutrophilic Spongiosis With Perivascular Neutrophils**

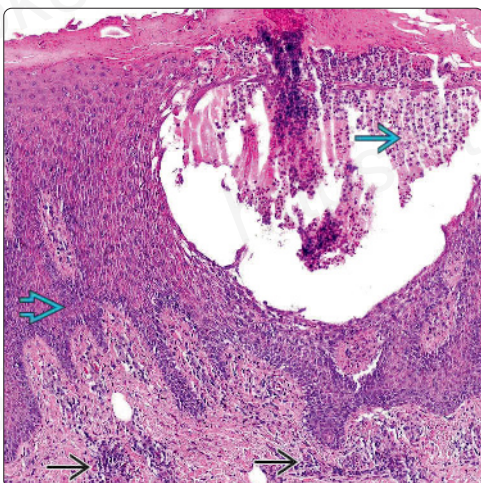


**Psoriasiform Hyperplasia With Neutrophilic Pustule Formation**

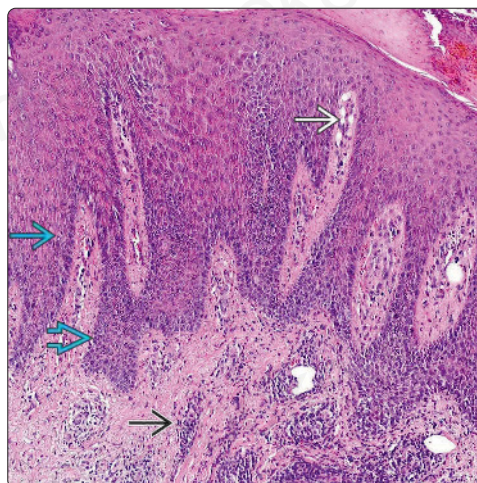


(Left) At higher magnification, the epidermal neutrophilic infiltrate is associated with massive spongiosis. A superficial perivascular lymphocytic inflammation with scattered neutrophils is present in the dermis. (Right) This biopsy of KB shows a psoriasiform epidermal acanthosis with intraepidermal neutrophilic pustule formation on acral skin. The dermis shows a mild mixed perivascular inflammatory infiltrate. These findings are strikingly similar to the histologic findings in pustular psoriasis.

**Higher Power View of Neutrophilic Pustule in Acral Skin**



**Psoriasiform Hyperplasia, Dilated Vessels, and Mixed Dermal Infiltrate**



(Left) Medium magnification shows epidermal acanthosis, neutrophilic pustule formation within the epidermis, and a perivascular mixed infiltrate with neutrophils in the dermis. (Right) Psoriasiform epidermal hyperplasia with an epidermal neutrophilic infiltrate and dilated vessels in the superficial dermis make KB appear very similar to psoriasis involving acral skin. A mixed infiltrate of lymphocytes, histiocytes, and neutrophils is present in the superficial dermis.



## Parapsoriasis

## KEY FACTS

## TERMINOLOGY

- Chronic, idiopathic cutaneous lymphoproliferative dermatitis divided into small plaque parapsoriasis [(SPP) < 5 cm] and large plaque parapsoriasis [(LPP) > 5 cm] variants
- Thought to exist on spectrum with pityriasis lichenoides chronica, pityriasis lichenoides et varioliformis acuta, lymphomatoid papulosis, and mycosis fungoides (MF)/cutaneous T-cell lymphoma (CTCL)

## CLINICAL ISSUES

- Oval, round, or irregular brown-red patches with fine or wrinkled scale
  - Asymptomatic or mildly pruritic
- Favors trunk, buttocks, flexures, and lower extremities
- SPP defined as < 5 cm
- LPP defined as > 5 cm
- SPP parapsoriasis
  - Rarely, if ever, progresses to MF/CTCL
- LPP

- 10-30% per decade progress to MF/CTCL

## MICROSCOPIC

- SPP may be pathologically indistinct from other spongiotic dermatoses, so clinicopathologic correlation is required
- LPP shares many features with MF but lacks full histopathological criteria to diagnose MF

## TOP DIFFERENTIAL DIAGNOSES

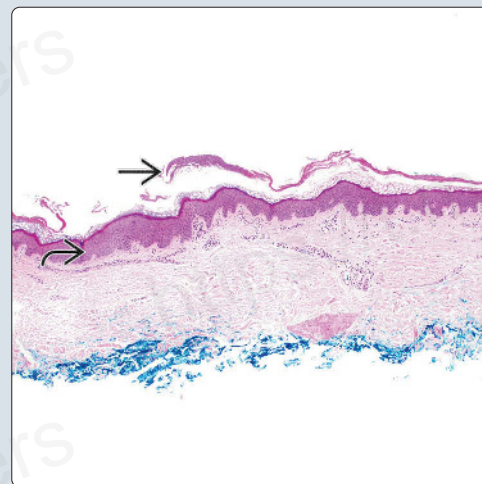
- Pityriasis rosea
- Pityriasis lichenoides
- Mycosis fungoides
- Secondary syphilis
- Poikilodermatous autoimmune connective tissue disease vs. poikilodermatous genodermatoses
- Nummular dermatitis
- Drug reaction (PR- or MF-like)
- Psoriasis

Cigarette Paper Wrinkling Atrophy  
Accentuated Upon Skin Stretching

(Left) Parapsoriasis on a man's buttock with cigarette paper wrinkling atrophy [A] was accentuated on stretching of the skin. Fine telangiectasia and mild reddish discoloration can be appreciated. It was present only on non-sun-exposed skin. (Right) Low-power image demonstrates mild parakeratosis [B] and acanthosis [C].

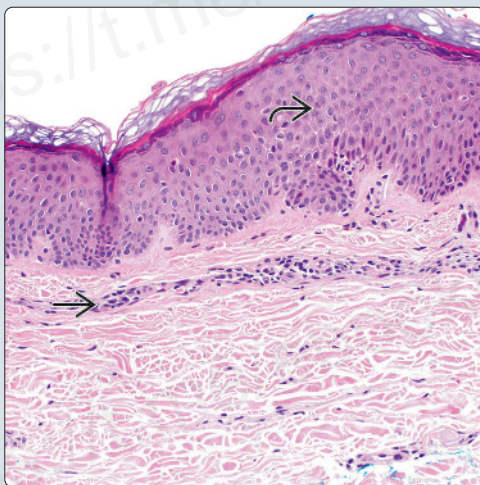


## Mild Acanthosis and Parakeratosis

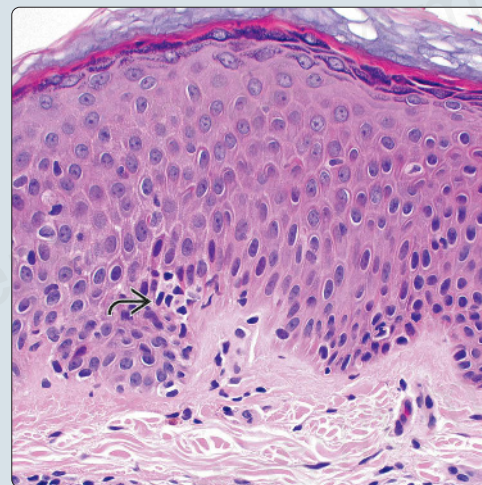


## Mild Spongiosis

(Left) Within the acanthotic epidermis there is mild spongiosis [D]. The dermis displays a nonspecific lymphocytic superficial infiltrate [E]. (Right) Exocytosis is the migration of nonneoplastic lymphocytes [F] within the epidermis.



## Exocytosis



## TERMINOLOGY

### Definitions

- Chronic, idiopathic cutaneous lymphoproliferative dermatitis divided into small plaque parapsoriasis (SPP) and large plaque parapsoriasis (LPP) variants

## ETIOLOGY/PATHOGENESIS

### Unknown

- Cutaneous lymphoproliferative disorder composed of CD4(+) T cells
  - Thought to exist on spectrum with pityriasis lichenoides chronica, pityriasis lichenoides et varioliformis acuta, lymphomatoid papulosis, and mycosis fungoides (MF)/cutaneous T-cell lymphoma (CTCL)
    - Not all authors/dermatologists agree on its existence

## CLINICAL ISSUES

### Epidemiology

- Age
  - Most commonly presents in middle age but can occur at all ages in all races
- Sex
  - Male predilection

### Site

- Favors trunk, buttocks, flexures, and lower extremities

### Presentation

- Symptomatology
  - Asymptomatic or mildly pruritic
- Morphology
  - Oval, round, or irregular brown-red patches with fine or wrinkled scale
  - SPP defined as < 5 cm
  - LPP defined as > 5 cm
    - LPP may demonstrate poikiloderma
  - Rare digitate and retiform variants exist

### Treatment

- Drugs
  - Topical corticosteroids (1st line)
- Radiation
  - Sunlight
  - Ultraviolet B phototherapy: Broadband or narrowband
  - Psoralen plus UVA phototherapy

### Prognosis

- Persists for years to decades
- SPP
  - Rarely, if ever, progresses to MF/CTCL
- LPP
  - 10-30% per decade progress to MF/CTCL

## MICROSCOPIC

### Histologic Features

- SPP
  - Nonspecific mild spongiotic dermatitis
    - Superficial lymphocytic infiltrate
    - Mild acanthosis

- Focal parakeratosis
- LPP
  - Interface and lichenoid dermatitis with overlap features of patch stage MF
    - Psoriasiform epidermal hyperplasia ± mild orthokeratosis or parakeratosis
    - Vacuolization in basal keratinocyte layer
    - Sparse dermal cellular infiltrate
    - Focal lymphocytic exocytosis
      - Pautrier microabscesses are usually absent
  - Poikilodermatous variant
    - Epidermal atrophy
    - Telangiectasia
    - Pigment incontinence

## ANCILLARY TESTS

### Immunohistochemistry

- Normal CD4/CD8 ratio

## DIFFERENTIAL DIAGNOSIS

### Pityriasis Rosea

- Look for herald patch
- Resolution of lesions within 6 weeks

### Pityriasis Lichenoides

- Lesions are rarely < 1 cm, more widely distributed
- Usually regresses over weeks to months

### Mycosis Fungoides

- Epidermotropism more prominent
- Pautrier microabscesses

### Secondary Syphilis

- Organism specific stains and serologies should identify *Treponema pallidum*
- Plasma cells may be present in inflammatory infiltrate
- Palmar and widespread lesions seen in secondary syphilis

### Poikilodermatous Autoimmune Connective Tissue Disease (e.g., Dermatomyositis) vs. Poikilodermatous Genodermatoses

- Pathology may be identical, requires clinical and serologic exclusion of these diseases

### Nummular Dermatitis

- More pruritic with more prominent scale or oozing
- Eosinophils may be present

### Drug Reaction (PR- or MF-Like)

- May see more eosinophils within inflammatory infiltrate

### Psoriasis

- Neutrophils within epidermis
- Thicker plaques with more prominent scale

## SELECTED REFERENCES

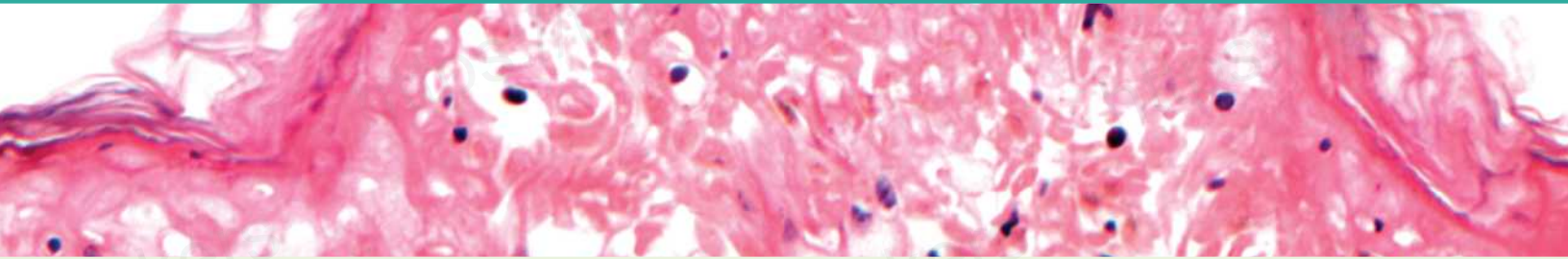
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## SECTION 2

# Lichenoid and Vacuolar Interface Dermatoses



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## KEY FACTS

### CLINICAL ISSUES

- Pruritic, planar, purple, and polygonal papules (5 Ps) commonly on wrists and shins of middle-aged adults
- Can affect scalp, nails, and mucous membranes
- Persists for months and in some cases years but tends to resolve within 6-18 months

### MICROSCOPIC

- Compact hyperkeratosis without parakeratosis
- Hypergranulosis, often wedge-shaped
- Lichenoid inflammatory infiltrate with interface dermatitis
- "Saw-toothed" rete ridges

### TOP DIFFERENTIAL DIAGNOSES

- Clinical
  - Lichenoid drug eruption
    - Clinical history can aid in diagnosis
  - Secondary syphilis

- Screening for RPR/VDRL and confirmation with FTA-ABS treponemal testing can help
- Pityriasis rosea
  - Presents with herald patch followed by secondary eruption of small scaly patches in Christmas tree distribution
- Histologic
  - Lichenoid drug eruption
    - More likely to have eosinophils and parakeratosis
  - Benign lichenoid keratosis (BLK)
    - Clinical history important
      - BLK is usually a single lesion (vs. lichen planus)
  - Lupus erythematosus
    - More likely to have epidermal atrophy, follicular plugging, dermal mucin
    - Serologies and direct immunofluorescence can aid in diagnosis

Polygonal Pruritic Papules



Hyperkeratotic Plaque

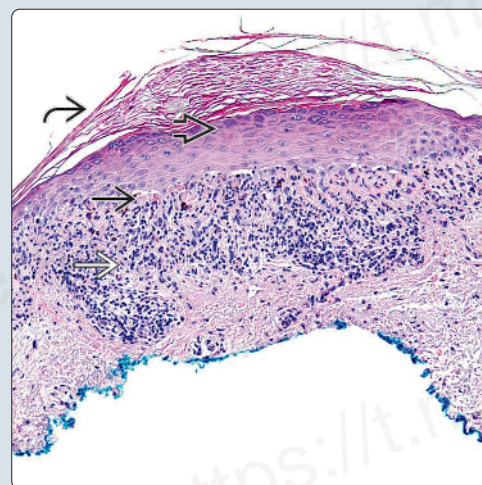


(Left) Lichen planus (LP) presents as multiple scattered flat-topped, erythematous and polygonal papules involving the flexor surface of the bilateral wrists. Note the koebnerization effect. (Courtesy D. Loo, MD.) (Right) Hypertrophic lichen planus (LP) can present as a well-demarcated hypertrophic plaque on the ankle with follicular plugs. It often clinically and histologically mimics lichen simplex chronicus.

Lichenoid Infiltrate



Lichenoid Interface Dermatitis



(Left) LP on low power shows a lichenoid interface dermatitis with a band-like infiltrate involving the dermoepidermal junction and compact hyperkeratosis. (Right) LP demonstrates compact hyperkeratosis, hypergranulosis, saw-toothed rete ridges, and a band-like inflammatory infiltrate.

## TERMINOLOGY

### Abbreviations

- Lichen planus (LP)

### Definitions

- Idiopathic, acute and chronic, inflammatory lichenoid dermatosis involving skin, hair, nails, &/or mucous membranes characterized by flat-topped violaceous, pruritic, and polygonal papules

## ETIOLOGY/PATHOGENESIS

### Unknown

- Some studies suggest that activated T cells recognize antigens on surface of basal keratinocytes
- More patients with lichen planus have hepatitis C than in controls
- Drug-induced lichenoid eruptions: Antihypertensives, diuretics, antimalarials

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - 0.5-1% in United States
- Age
  - Middle-aged adults, usually 4th-7th decades of life
- Sex
  - Female > male (3:2 ratio)

### Site

- Flexor surface of wrists, forearms, dorsal hands, shins, lumbar region, glans penis, scalp, and mouth

### Presentation

- Skin
  - 5 Ps: Pruritic, planar (flat-topped), purple, and polygonal papules commonly on wrists and shins
  - Wickham striae: Fine reticulate network of white lines, corresponding to periadnexal hypergranulosis
  - Worsening pruritus with increased body surface area involvement, as well as with hypertrophic variant of shins
  - In children, lesions are often linear or zosteriform and generally without mucosal involvement
  - Koebnerization (induction by trauma) is common and may yield linear lesions
  - Numerous variants exist
  - Actinic LP (also called LP actinicus, LP subtropicus, LP tropicus, lichenoid melanodermitis)
    - More common in persons of Middle Eastern descent
    - Occurs on sun-exposed skin (face, neck, flexor surfaces of forearms and hands)
    - Appears as red-brown annular plaques with surrounding hypopigmentation
  - Acute LP (also called exanthematous or eruptive LP)
    - Disseminated form involving trunk, inner aspects of wrists, and dorsum of feet with resolution within 3-6 months, often with subsequent hyperpigmentation
  - Annular LP
    - Occurs as annular lesions in about 10% of patients with LP and involves intertriginous areas (axilla, groin) and vermillion of lips

- Atrophic LP
  - Commonly involves lower leg, closely resembles lichen sclerosus clinically and, in some cases, porokeratosis
  - Patients may also have pseudopelade (form of cicatricial alopecia)
- Annular atrophic LP
  - Involves same regions as common LP but with enlarging purple plaques with atrophic center
- LP pemphigoides
  - Bullae located on limbs, with circulating IgG autoantibodies against 180 kDa BP antigen
    - ◻ DIF reveals linear band of IgG and C3 along junction, distinguishing LP pemphigoides from bullous LP
- Bullous LP
  - Bullae located on lower extremities
  - Often due to longstanding LP with exaggeration of Max-Joseph spaces histopathologically
    - ◻ No autoantibody mediated blistering
- Hypertrophic LP (also called LP verrucosus)
  - Usually presents as symmetric lesions on anterior shins due to chronic rubbing, lasting on average 6 years duration
  - Features of lichen simplex can be appreciated histopathologically
  - Squamous cell carcinoma can occur in this variant
- Linear LP
  - Lichenoid purple papules occurring spontaneously along lines of Blaschko, usually seen in patients in their late 20s or early 30s
- LP-lupus erythematosus overlap syndrome
  - Usually involves acral sites or extremities
  - Patients present with features of both LP and lupus erythematosus (including elevated antinuclear antibody titer and other lupus serologies)
- LP pigmentosus
  - Presents on face, neck, flexural folds in reticular pattern as gray to brown macules and papules
  - Histopathologically indistinguishable from erythema dyschromicum perstans
  - More common in Hispanic and Indian populations
- Ulcerative LP
  - Presents as ulcers and erosions of palms, soles, and mucosal membranes
  - Slightly increased risk of malignant transformation
- Vulvovaginal gingival syndrome
  - Presents as desquamative or erosive lesions involving vulva, vagina, and gingiva
- Scalp
  - Lichen planopilaris (LPP)
    - More common in women and presents as scarring alopecia with follicular keratotic papules, perifollicular erythema and tufting/polytrichia
    - May have scalp pruritus
  - Frontal fibrosing alopecia
    - Scarring alopecia mainly seen in postmenopausal women along frontoparietal region and eyebrows
  - Graham Little syndrome
    - LPP of scalp with alopecia of axilla and groin, along with keratosis pilaris of trunk and extremities
- Nails



- Trachyonychia, twenty-nail dystrophy; may spare skin, especially in children
- Nail changes seen in 5-10% of patients with LP; longitudinal fissures and dorsal pterygium formation
- Mucous membranes
  - Large percentage of patients with cutaneous LP have mucous membrane involvement
  - Some studies associate oral LP with chronic liver disease (especially hepatitis C)
  - Children seem to rarely be affected with this form
  - Some reports suggest women are affected 2x as often as men
  - At least 6 forms of oral LP exist
  - Reticular
    - Most common form presents as white lacy stria usually involving buccal mucosa symmetrically
    - Gingival involvement common
  - Atrophic
    - Painful lesions that present as red patches with edge of white striae
  - Papular
    - Presents as pinpoint white papules that can affect glans penis
  - Plaque
    - Presents as slightly elevated and homogeneously white plaques
    - Frequently occurs in tobacco smokers
  - Bullous
    - Presents as small vesicles and bullae
  - Erosive
    - Presents as irregular erosions with white to yellow exudate
    - May lead to desquamative gingivitis

## Treatment

- Drugs
  - First rule out drug eruption mimicking LP
  - Topical and intralesional therapies
    - Corticosteroids, retinoids, cyclosporine, tacrolimus, pimecrolimus, acitretin, PUVA/UVB
  - Systemic therapy
    - Cyclosporine, dapsone, alefacept, mycophenolate mofetil, thalidomide, metronidazole, hydroxychloroquine, azathioprine, cyclophosphamide, griseofulvin, methotrexate, enoxaparin

## Prognosis

- Persists for months and in some cases years but tends to resolve within 6-18 months

## MICROSCOPIC

### Histologic Features

- Lichenoid interface dermatitis: (Band-like) inflammatory infiltrate obscures the dermoepidermal junction
  - Infiltrate composed predominantly of CD4(+) helper lymphocytes often with melanin incontinence
  - May see eosinophils in hypertrophic LP and in drug-induced lichenoid eruptions
- Compact hyperkeratosis without parakeratosis (except with trauma)

- Hypergranulosis, classically wedge shaped and may surround follicles or acrosyringia
- Irregular acanthosis exhibiting "saw-toothed" rete ridges
- Individually necrotic keratinocytes (Civatte bodies)
- Basal keratinocyte liquefaction and degeneration with colloid bodies (necrotic keratinocytes in dermis) often present

## ANCILLARY TESTS

### Immunofluorescence

- Predominantly IgM and less frequently IgA, IgG, C3, and fibrin staining of colloid bodies

## DIFFERENTIAL DIAGNOSIS

### Clinical

- Skin (top 3)
  - Lichenoid drug reaction
    - Tends to be more eczematous &/or psoriasiform in appearance with predilection for sun-exposed areas
  - Secondary syphilis
    - Presents as papulosquamous eruption on trunk and extremities
    - Screening for RPR/VDRL and confirmation with FTA-ABS treponemal testing can help
  - Pityriasis rosea
    - Occurs predominantly in children and young adults
    - Presents with herald patch followed by secondary eruption of small scaly patches in Christmas tree distribution

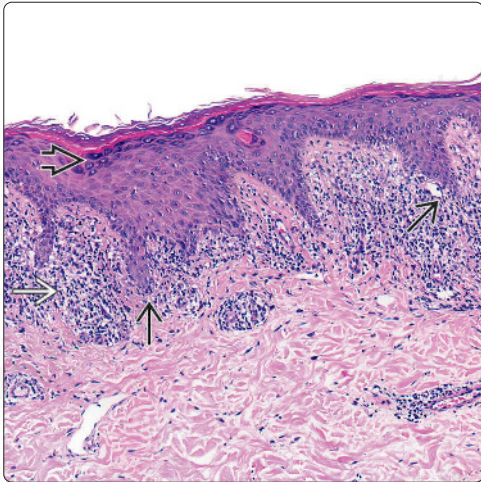
### Histopathological

- Lichenoid drug eruption
  - Similar lichenoid interface dermatitis as LP but classically has eosinophils and parakeratosis
- Benign lichenoid keratosis (BLK)
  - Lichenoid interface dermatitis, which may have parakeratosis and, rarely, eosinophils
  - Solar lentigo is commonly adjacent to this lesion
  - Clinical history important
    - BLK is usually single lesion (vs. LP)
- Lupus erythematosus
  - Lichenoid interface dermatitis
  - Rarely with parakeratosis or eosinophils
  - Direct immunofluorescence with full house continuous band of immunoglobulins IgG, IgA, IgM, and C3 at basement membrane zone
- Squamous cell carcinoma
  - Hypertrophic LP may be mistaken for SCC or keratoacanthoma (KA)
  - p53 overexpression and perforating elastic fibers seen in KA or SCC

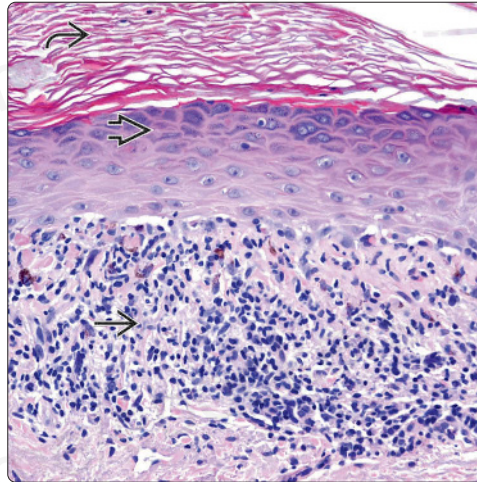
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"Saw-Tooth" Rete

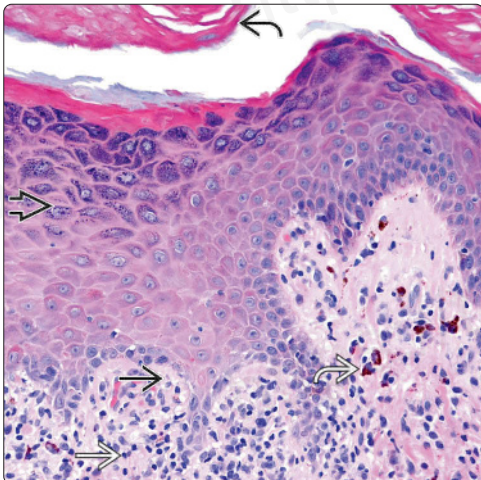


Hypergranulosis and Hyperkeratosis

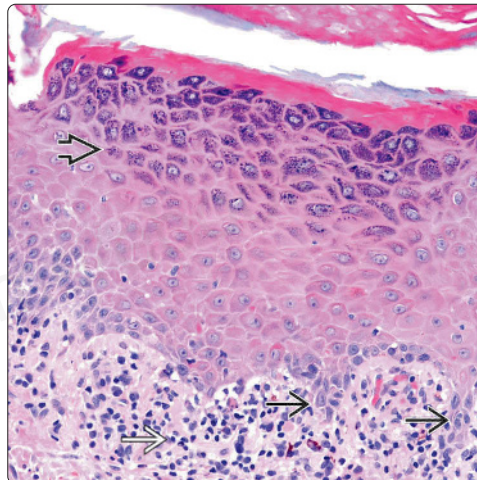


(Left) Another example of LP demonstrates "saw-toothed" rete ridges [box], a lichenoid inflammatory infiltrate [box], and hypergranulosis [box]. (Courtesy UCSF Dermatopathology Service.) (Right) LP again shows compact hyperkeratosis [box], hypergranulosis [box] and a band-like inflammatory infiltrate [box].

Wedge-Shaped Hypergranulosis

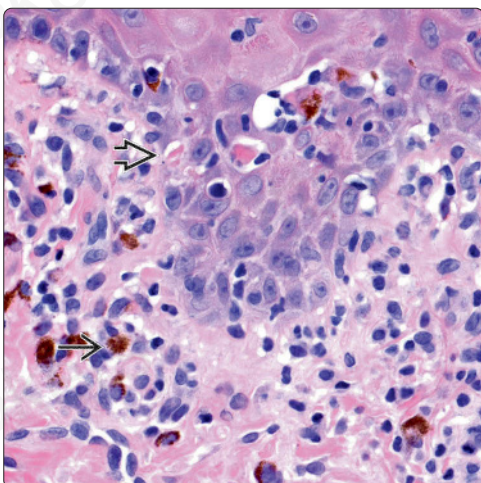


Wedge-Shaped Hypergranulosis

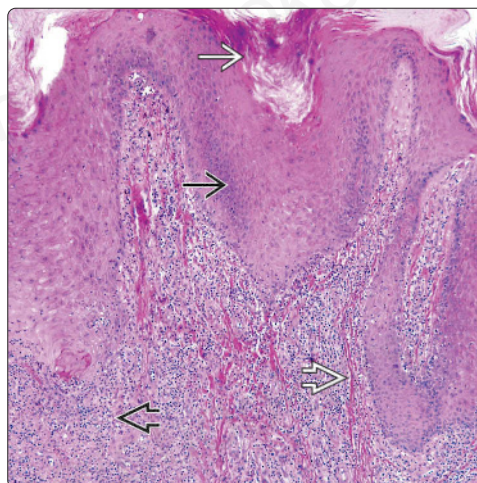


(Left) LP often demonstrates compact hyperkeratosis [box], wedge-shaped hypergranulosis [box], "saw-toothed" rete ridges [box] and a band-like inflammatory infiltrate [box] with accompanying pigment incontinence [box]. (Right) LP often demonstrates wedge-shaped hypergranulosis [box], "saw-toothed" rete ridges [box], and a band-like inflammatory infiltrate [box].

Interface Dermatitis



Hypertrophic Lichen Planus



(Left) High power of LP shows liquefactive degeneration of the basal layer [box] with adjacent lymphocytic infiltrate and accompanying pigment incontinence [box]. (Right) Hypertrophic LP shows prominent epidermal hyperplasia [box], orthokeratosis [box], psoriasiform hyperplasia often at the margins, "streaked collagen" [box], and a lichenoid inflammatory infiltrate [box] sometimes less dense than LP and often concentrated at tips of rete ridges.



## KEY FACTS

### TERMINOLOGY

- Benign lichenoid keratosis, lichen planus-like keratosis, involuting lichenoid plaque, solitary lichen planus

### CLINICAL ISSUES

- Upper extremities and trunk
- Solitary circumscribed papule or plaque up to 1 cm in diameter
- Erythematous or violaceous ± scale
- Pruritus &/or burning sensation

### MICROSCOPIC

- Characterized by dense lichenoid band of predominantly lymphocytes and histiocytes
- Usually acanthotic with scattered apoptotic keratinocytes
- Interface vacuolar change, Civatte bodies, and pigment incontinence
- Hyperkeratosis with orthokeratosis or parakeratosis

- May see discernible keratosis or lentigo to side of inflammatory infiltrate

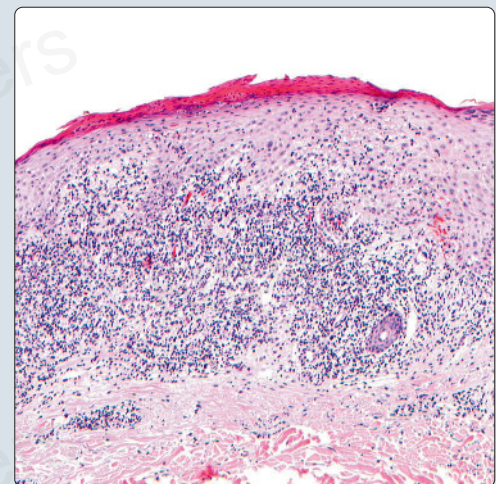
### TOP DIFFERENTIAL DIAGNOSES

- Histopathologic differential diagnosis
  - Lichen planus
  - Lichenoid actinic (solar) keratosis
  - Lichenoid drug eruption
  - Fixed drug eruption
  - Erythema multiforme
- Clinical differential diagnosis
  - Seborrheic keratosis
  - Lichen planus
  - Nonmelanoma skin cancer (squamous cell carcinoma in situ or superficial basal cell carcinoma)

Lichenoid Keratosis

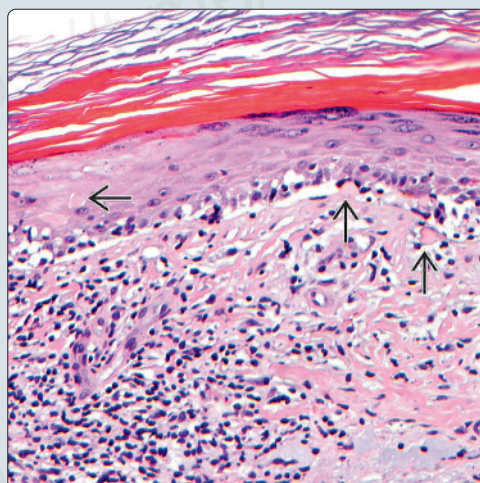


Lichenoid Lymphocytic Infiltrate

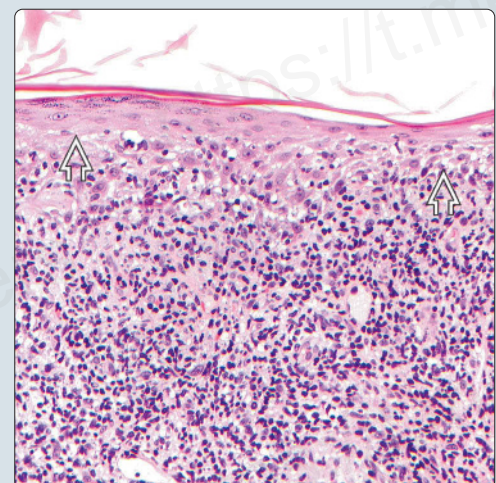


(Left) Biopsy-proven lichenoid keratosis presented as a keratotic, light pink, 1-cm plaque on the breast of this female patient. (Right) Lichenoid keratosis is characterized by a single lesion with a lichenoid lymphocytic infiltrate.

Vacuolar Interface Change



Epidermal Atrophy



(Left) Vacuolar interface change along the dermal-epidermal junction is a universal finding. Civatte (colloid) bodies may be found along the dermal-epidermal junction or within the keratinocyte layer. (Right) If the lesion is longstanding, the epidermis may atrophy secondary to repeated destruction of basal cells by the inflammatory infiltrate.



## TERMINOLOGY

### Synonyms

- Benign lichenoid keratosis, lichen planus-like keratosis, involving lichenoid plaque, solitary lichen planus

### Definitions

- Keratosis with lichenoid band of inflammation

## ETIOLOGY/PATHOGENESIS

### Reactive Condition

- Preexisting lesion usually present
  - e.g., solar lentigo or seborrheic keratosis
- Sensitization to lesion occurs
- Cell-mediated immune response ensues
- Biopsy occurs after immune-mediated destruction has started
  - Original lesion may or may not be discernible

## CLINICAL ISSUES

### Epidemiology

- Age
  - Middle-aged and older adults
- Sex
  - More common in females

### Site

- Upper extremities and trunk
  - Rarely on face

### Presentation

- Solitary circumscribed papule or plaque up to 1 cm in diameter
  - Minority of cases may have multiple lesions
  - Erythematous or violaceous
- Appears suddenly
- Pruritus &/or burning sensation
- ± scale

### Treatment

- Cryotherapy

### Prognosis

- Does not tend to recur

## MACROSCOPIC

### Dermoscopy

- Progressive regression of original lesion

## MICROSCOPIC

### Histologic Features

- Characterized by dense lichenoid band of predominantly lymphocytes and histiocytes
  - Occasional plasma cells, neutrophils, &/or eosinophils may be present
  - Obscures dermal-epidermal junction
- May see discernible keratosis or lentigo to side of inflammatory infiltrate
- Interface vacuolar change is present
- Usually acanthotic with scattered apoptotic keratinocytes

- Eosinophilic colloid bodies
  - Contain IgM and fibrin
- Pigment incontinence (mild to heavy)
- Hyperkeratosis
  - Orthokeratosis or parakeratosis
- Variants
  - Atrophic
    - Papillary dermal fibrosis (scarring)
    - Thinning of epidermis
  - Atypical (mycosis fungoides-like)
    - Lymphocytic Pautrier-like microabscesses
    - Lymphocytes line up along dermal-epidermal junction
    - Epidermotropism of lymphocytes
  - Toxic epidermal necrolysis-like
    - Confluent necrosis of epidermis
    - Causes separation along dermal-epidermal junction
  - Bullous
    - Separation of epidermis from dermis creating bulla

## ANCILLARY TESTS

### Immunohistochemistry

- Caution
  - Melan-A has been reported to stain nests of keratinocytes in these lesions
    - Can cause confusion with melanocytic neoplasms

## DIFFERENTIAL DIAGNOSIS

### Histopathologic Differential Diagnosis

- Lichen planus
  - Widespread eruption favoring flexor surfaces of extremities
  - May involve oral mucosa
  - No parakeratosis
- Lichenoid actinic (solar) keratosis
  - Must have epithelial atypia, usually confined to basal layer of epidermis
- Lichenoid drug eruption
  - Grouped papules or psoriasiform-appearing lesions
  - More eosinophils than lichenoid keratosis
- Fixed drug eruption
  - Superficial and deep infiltrate with vacuolar alteration
  - Eosinophils usually present
  - More numerous neutrophils
- Erythema multiforme
  - Clinical history is strikingly different
  - Not discrete solitary lesion
  - Vacuolar rather than lichenoid interface dermatitis

### Clinical Differential Diagnosis

- Seborrheic keratosis
- Lichen planus
- Nonmelanoma skin cancer (squamous cell carcinoma in situ or superficial basal cell carcinoma)

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## KEY FACTS

### TERMINOLOGY

- Erythema multiforme (EM) minor (von Hebra): Typical targetoid skin lesions with mild or no mucous membrane involvement
- Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN): Serious, life-threatening reaction; extensive epidermal necrosis with severe mucous membrane involvement and systemic symptoms

### ETIOLOGY/PATHOGENESIS

- Fas ligand-mediated apoptosis probably central to development of epidermal necrosis

### MICROSCOPIC

- EM minor
  - Orthokeratotic stratum corneum as seen in acute process
  - Superficial, sparse perivascular lymphohistiocytic infiltrate with lymphocyte exocytosis

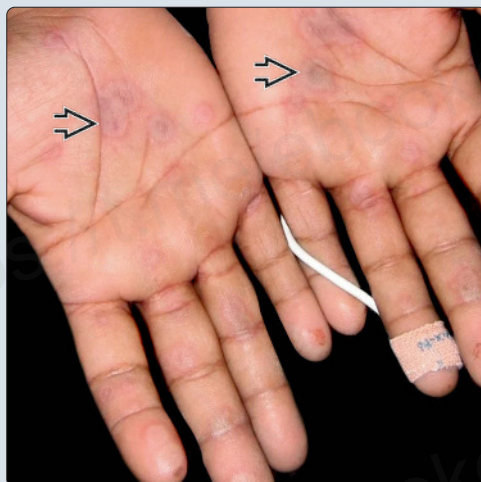
- Interface dermatitis consisting of lymphocytes along dermal-epidermal junction with basilar vacuolization
- SJS/TEN
  - Well-developed lesions display marked keratinocyte necrosis leading to full-thickness epidermal necrosis with subepidermal bulla formation
  - Interface changes and apoptotic keratinocytes can also affect hair follicles and eccrine duct epithelium

### TOP DIFFERENTIAL DIAGNOSES

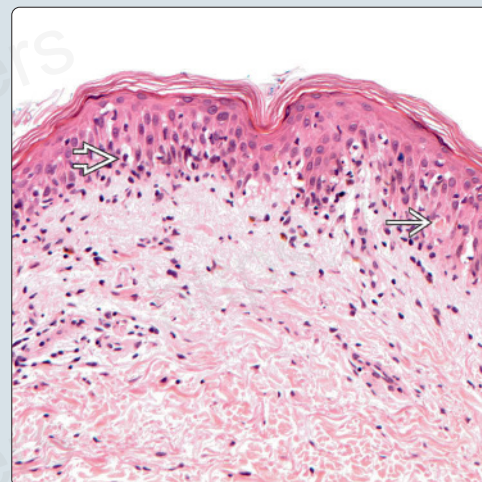
- Fixed drug eruption
- Acute graft-vs.-host disease
- Pityriasis lichenoides et acuta
- Phototoxic dermatitis
- Connective tissue disease

Targetoid Macules

(Left) Erythema multiforme (EM) presents as targetoid macules with palmar involvement. (Courtesy M. Chiu, MD.) (Right) EM shows superficial lymphocytic inflammation predominantly along the dermal-epidermal junction leading to basal vacuolar change with scattered necrotic keratinocytes.

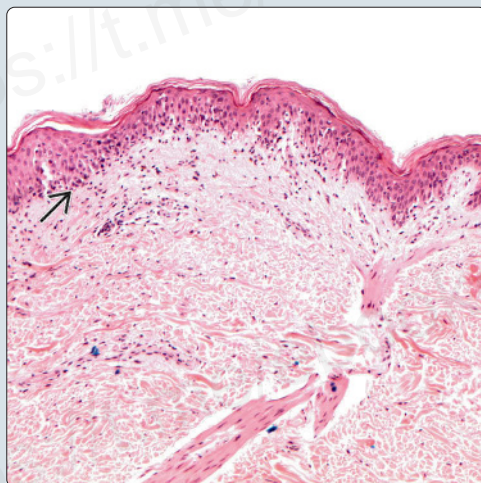


Interface With Vacuolar Change

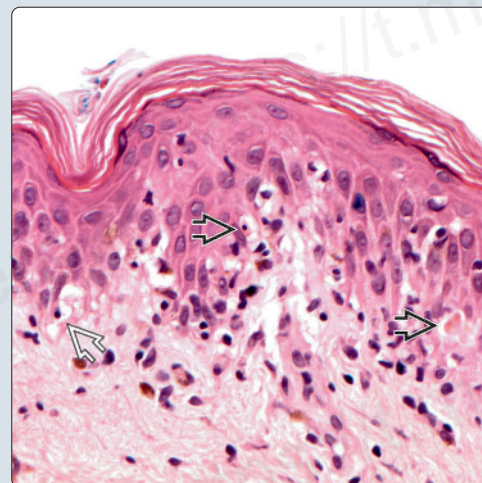


Necrotic Keratinocytes

(Left) EM demonstrates a superficial lymphocytic inflammation with interface change along the dermal-epidermal junction. Epidermal spongiosis and necrotic keratinocytes confined to the lower portions of the epidermis are also typically present. (Right) EM on higher power demonstrates interface change along the dermal-epidermal junction characterized by clear spaces around keratinocytes. Also note the necrotic or apoptotic keratinocytes.



Dyskeratosis



## TERMINOLOGY

### Abbreviations

- Erythema multiforme (EM)
- Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)

### Synonyms

- EM minor
  - EM von Hebra, herpes simplex-associated EM
- SJS/TEN
  - Lyell syndrome

### Definitions

- EM minor (von Hebra): Acute, self-limited, immune-mediated reaction to infections or drugs consisting of typical targetoid skin lesions with mild or no mucous membrane involvement
- SJS/TEN: Serious, life-threatening reaction often to medications consisting of atypical targetoid lesions that evolve to extensive epidermal necrosis and epidermal sloughing with severe mucous membrane involvement and systemic symptoms
  - SJS: 10% of total body surface area affected
  - TEN: 30% of total body surface affected

## ETIOLOGY/PATHOGENESIS

### Infectious Agents (Major Causes of EM Minor)

- Herpes simplex virus types 1 and 2
- Mycoplasma pneumoniae

### Drug Mediated (Major Causes of SJS/TEN)

- Sulfonamides
- Antibiotics
  - Aminopenicillins, cephalosporins, quinolones
- Anticonvulsants
  - Phenytoin, barbiturates, carbamazepine
- Nonsteroidal antiinflammatory medications
  - Phenylbutazone, oxyphenbutazone, isoxicam, piroxicam

### Other Associations

- Environmental factors, radiocontrast media, connective tissue disease, neoplasms, pregnancy, vaccinations

### Pathogenesis of SJS/TEN

- Fas ligand-mediated apoptosis is probably central to development of epidermal necrosis

## CLINICAL ISSUES

### Presentation

- EM minor
  - Typically young adults affected; uncommon in childhood
  - Targetoid lesions consisting of well-demarcated plaques with 3 distinct zones
    - (1) Central dusky portion
    - (2) Surrounding halo of pallor
    - (3) Rim of erythema
  - Cutaneous lesions primarily on face and extensor extremities
- SJS/TEN
  - Any age group can be affected

- Early painful atypical targetoid lesions consisting of edematous palpable plaques with only 2 zones and poorly defined border
- Rapid evolution of atypical targetoid lesions into bulla that erode and ulcerate, leaving affected skin surface denuded
- Mucous membranes affected in same way as cutaneous surface
- Systemic symptoms include fever, myalgias, sore throat, headache, leukopenia, anemia

### Treatment

- EM minor
  - If self-limited, symptomatic treatment with antihistamines, topical corticosteroids, topical Benadryl
  - If recurrent, can prophylactically treat with antivirals such as acyclovir or valacyclovir
- SJS/TEN
  - Supportive care for loss of skin barrier, including maintaining fluid balance, nutrition, and prevention of sepsis
  - Studies support benefit of intravenous immunoglobulin (IVIG); there is controversy regarding use of systemic steroids or other immunosuppressive agents

### Prognosis

- EM minor
  - Acute lesions last approximately 2 weeks then resolve over 6 weeks; can be recurrent, especially in cases caused by herpes simplex
- SJS/TEN
  - Mortality ranges from 5-40% depending on extent of epidermal involvement
  - Poorer prognosis with increased age and decreased renal function
  - Major cause of death is from sepsis, particularly in cases related to *Staphylococcus aureus* or *Pseudomonas aeruginosa*

## MICROSCOPIC

### Histologic Features

- EM minor
  - Orthokeratotic stratum corneum as seen in acute process
  - Mild epidermal spongiosis with papillary dermal edema
  - Superficial, sparse perivascular lymphohistiocytic infiltrate with lymphocyte exocytosis
  - Interface dermatitis consisting of lymphocytes along dermal-epidermal junction with basilar vacuolization
  - Necrosis of individual keratinocytes along basal layer with varied intensity, possibly leading to intraepidermal or subepidermal vesicles
  - Absent to rare eosinophils, unless drug/medication related
- SJS/TEN
  - Early lesions with scattered apoptotic keratinocytes in basal layer similar to EM
  - Well-developed lesions contain numerous necrotic keratinocytes leading to full-thickness epidermal necrosis with subepidermal bulla formation



- Given acute nature of eruption, orthokeratotic basket weave stratum corneum overlies full-thickness epidermal necrosis
- Interface changes and apoptotic keratinocytes can also affect hair follicles and eccrine duct epithelium
- Compared to EM, there is less dermal inflammatory infiltrate, less epidermal lymphocytic exocytosis, and more epidermal necrosis

## DIFFERENTIAL DIAGNOSIS

### Clinical

- Fixed drug eruption
  - Presents as well-defined erythematous to dusky, macule, patch or plaque with site-specific predilection
  - Most common drug causes are NSAIDs, antibiotics, and sedatives
- Acute GVHD
  - Tends to present first on hands, feet, or face as tender erythematous macules, patches, papules, or plaques; can spread to involve whole body
- Pityriasis lichenoides et acuta
  - Likely hypersensitivity reaction to various infectious agents characterized by crusted erythematous papules
- Phototoxic dermatitis
  - Nonimmunologic, dose-dependent skin eruption in photodistributed areas of skin presenting as erythematous patches or plaques
- Connective tissue disease
  - Systemic lupus, discoid lupus, dermatomyositis, and scleroderma are examples that can present with erythematous papules, plaques, macules or patches (sometimes in photodistribution)

### Histologic

- Fixed drug eruption
  - As in EM, features include interface changes and necrotic keratinocytes mainly along dermal-epidermal junction; however, fixed drug eruption is distinguished by not only superficial but also deep mixed-cell infiltrate with eosinophils
  - As fixed drug tends to be more chronic, there are other epidermal changes including epidermal acanthosis, hyperkeratosis, and clusters of colloid bodies in rete ridges
  - Pigmented variants of fixed drug are also characterized by numerous papillary dermal melanophages
- Acute GVHD
  - Vacuolar alteration along dermal-epidermal junction with superficial lymphocytic dermal inflammation, lymphocyte exocytosis, and variable amounts of spongiosis
  - Interface changes typically also involve hair follicles (hair bulge particularly affected) and eccrine glands
  - Apoptotic keratinocytes at all levels of epidermis are associated with adjacent lymphocytes (satellite cell necrosis)
- Pityriasis lichenoides et acuta
  - Extensive basal layer vacuolar interface change with epidermal spongiosis and individual keratinocyte necrosis; epidermal acanthosis with overlying parakeratotic hyperkeratosis

- Dermal edema with varied density of perivascular inflammation usually extending into reticular dermis in wedge-shaped pattern
- Phototoxic dermatitis
  - Like EM, epidermal spongiosis with varying amounts of necrotic keratinocytes/epidermal necrosis; however, lacks interface changes and has superficial and deep mixed inflammation with more neutrophils
- Connective tissue disease (systemic lupus, discoid lupus, dermatomyositis, and scleroderma are examples)
  - Vacuolar alteration along dermal-epidermal junction, sometimes with scattered necrotic keratinocytes, and associated lymphohistiocytic infiltrate along superficial and deep vascular plexus as well as around adnexal structures
  - Distinguishing features include mucin deposition between collagen bundles and associated thickened basement membrane

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- EM minor
  - Early lesions with dermal edema, marked in papillary dermis, associated with superficial lymphocytic infiltrate and possible extravasation of red blood cells
  - Greater inflammatory changes than seen in SJS/TEN with more intense superficial dermal lichenoid inflammation
  - Leukocytoclasia and true vasculitis are absent
  - Subepidermal vesiculation can occur but is usually not associated with full-thickness epidermal necrosis
- SJS/TEN
  - Less inflammation and more extensive epidermal necrosis than in EM minor
  - Vacuolar change and keratinocyte apoptosis can also be seen along hair follicles and sweat duct epithelium (not seen in EM minor)
  - Important clinical differential includes staphylococcal scalded skin that is distinguished by subcorneal pustules

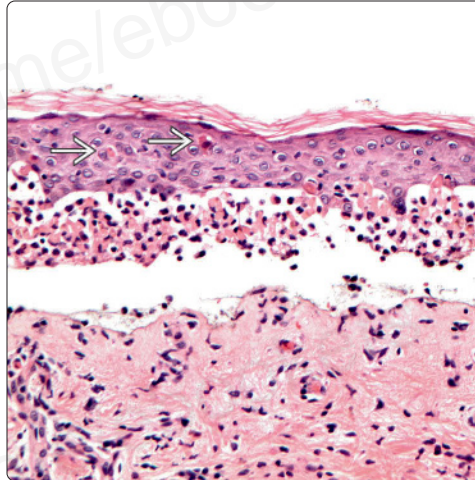
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**Toxic Epidermal Necrolysis**

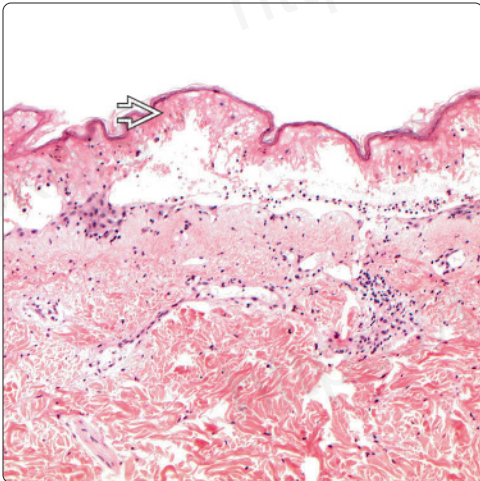


**Dyskeratosis in Upper Epidermis**

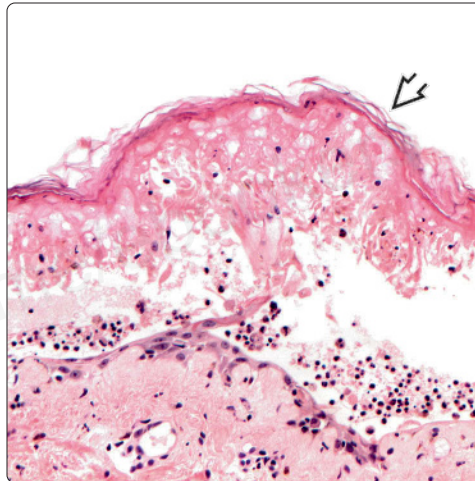


(Left) Toxic epidermal necrolysis (TEN) presents clinically as diffuse epidermal sloughing with involvement of the mucous membranes. (Courtesy H.R. Jalian, MD.) (Right) Another example of EM demonstrates denser inflammation leading to subepidermal bulla formation. Note that features of EM are still present, including scattered necrotic (apoptotic) keratinocytes.

**Toxic Epidermal Necrolysis**

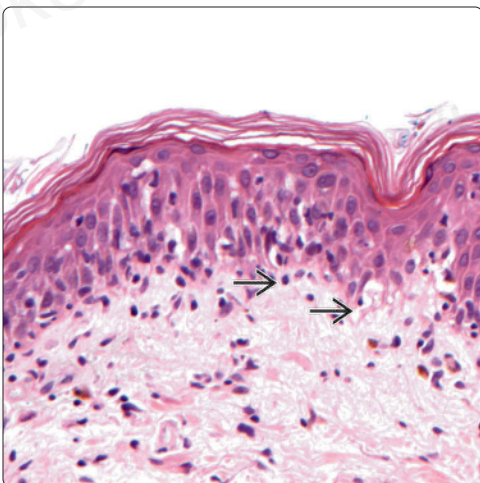


**Toxic Epidermal Necrolysis With Orthokeratosis**

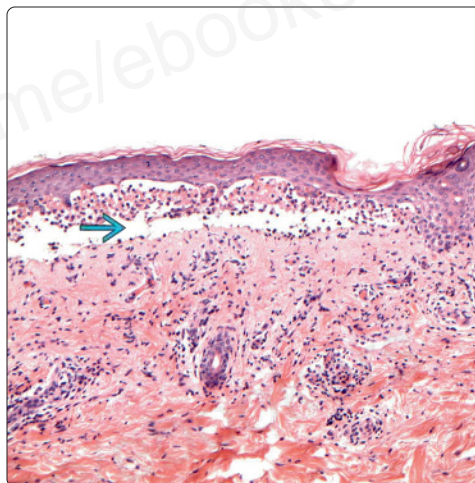


(Left) TEN also demonstrates superficial perivascular inflammation, but in contrast to EM there is full-thickness necrosis of the epidermis causing a subepidermal bullous split. (Right) Given the acute nature of TEN, an orthokeratotic "basket weave" stratum corneum overlies full-thickness epidermal necrosis with a subepidermal split and minimal inflammation.

**Basal Layer Vacuolization**



**Subepidermal Bulla**



(Left) Superficial lymphocyte predominant inflammation along dermal-epidermal junction leads to interface change characterized by basal vacuolization. (Right) Another example of EM demonstrates a dense inflammatory infiltrate leading to subepidermal bulla formation.



## KEY FACTS

### TERMINOLOGY

- Definition
  - Group of idiopathic disorders of unknown etiology characterized by petechiae and bronze discoloration of skin on lower extremities

### CLINICAL ISSUES

- More common in males; between 3rd-6th decades
- Usually bilateral purpuric lesions, on lower extremities (pretibial and on the ankles) but sometimes lower trunk and upper extremities
- Pigmented purpuric dermatoses has different clinical presentations and denominations but same histological findings

### MICROSCOPIC

- Main histologic finding is lymphocytic perivascular infiltrate limited to papillary dermis, which is sometimes between vessels, in band-like or lichenoid pattern

- Extravasated red blood cells (RBCs) and often subtle hemosiderin deposits are found in vicinity of capillaries
  - Vascular injury is usually minimal
- Older lesions show less dense infiltrate and capillaries often show dilatation of their lumen and proliferation of their endothelium
  - Extravasated RBCs may no longer be present, but one frequently finds hemosiderin deposition: Iron stain useful in these cases
- In eczematid-like purpura of Doucas and Kapetanakis, there is spongiosis and parakeratosis is more prominent
- Granulomatous variant shows superficial, nonnecrotizing granulomatous infiltrate, with extravasation of erythrocytes and hemosiderin deposition

### TOP DIFFERENTIAL DIAGNOSES

- Stasis dermatitis
- Atypical T-cell process
- Lichenoid dermatitis or lichenoid drug reaction

### Clinical Variants of Pigmented Purpuric Dermatoses

(Left) Several clinical forms are shown in this image: Eczematid-like purpura of Doucas and Kapetanakis [1], lichen aureus [2], and Gougerot-Blum disease [3]. (Right) Schamberg disease clinically shows clusters of pinhead-sized red macules [4] and barely palpable papules.

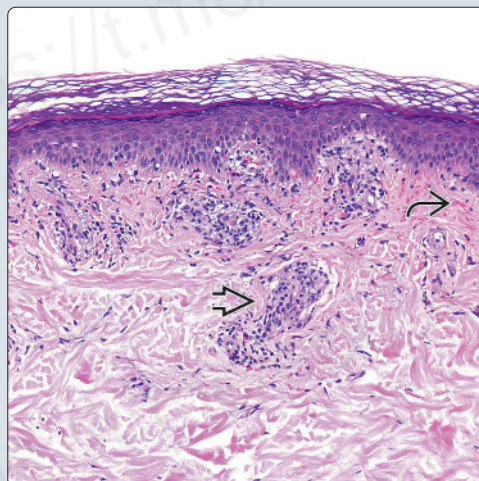


### Small Red Macules of Schamberg Disease

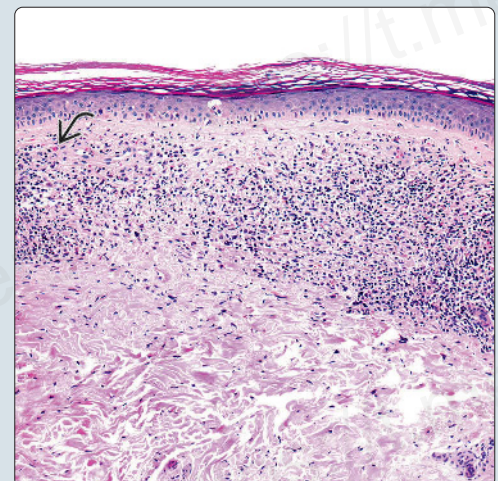


### Perivascular Lymphocytic Infiltrate of Schamberg Disease

(Left) Schamberg disease usually has mild to moderate dense perivascular lymphocytic infiltrate [1] and numerous extravasated red blood cells [2]. (Right) A dense lichenoid infiltrate and extravasated red blood cells [3] are seen in this case of lichen aureus.



### Lichenoid Infiltrate With Extravasated Erythrocytes





## TERMINOLOGY

### Abbreviations

- Pigmented purpuric dermatoses (PPD)

### Synonyms

- Capillaritis of unknown cause
- Purpura pigmentosa chronica
- Pigmented purpura
- Pigmented purpuric dermatitis
- Chronic purpuric dermatitis

### Definitions

- Group of idiopathic disorders of unknown etiology characterized by petechiae and bronze discoloration of skin on lower extremities

## CLINICAL ISSUES

### Epidemiology

- Age
  - 3rd-6th decades
- Sex
  - More common in males

### Presentation

- Mild pruritus may be present, but usually lesions are asymptomatic
- Usually bilateral, on lower extremities (pretibial and on ankles) but sometimes lower trunk and upper extremities
- PPD has several different clinical presentations and denominations but same histological findings
  - Schamberg disease (progressive pigmentary dermatosis): Clusters of pinhead-sized, reddish macules and barely palpable papules become confluent, coalescing into patches
  - Majocchi disease (or purpura annularis telangiectodes): Similar to Schamberg, but annular form and telangiectasias predominate
    - Sometimes can be arciform
  - Gougerot-Blum disease (pigmented purpuric dermatitis): Lichenoid papules, plaques, macules in association with lesions of Schamberg disease
  - Lichen aureus: Localized, 1 or few patches or plaques, rust-colored, purple, or golden, arising on extremities or trunk
    - Male predilection with peak incidence in 4th decade
  - Eczematid-like purpura of Doucas and Kapetanakis: Papules, scaling, and lichenification
  - Recently, unusual and rare granulomatous variant of PPD has been described: Affects almost exclusively patients of East Asian descent

### Treatment

- Phototherapy has been shown to be effective in some cases

### Prognosis

- Course is chronic (months to years), slow to evolve and resolve

## MACROSCOPIC

### General Features

- Dermoscopy shows pinpoint hemorrhages (purpura)
  - Young lesions are red; older lesions tan to brown (for degradation of hemoglobin to hemosiderin)
  - Overall color impression: Reddish brown, cayenne pepper

## MICROSCOPIC

### Histologic Features

- Main histologic finding is lymphocytic perivascular infiltrate limited to papillary dermis, which sometimes may infiltrate adjacent papillary dermis between vessels or assume band-like or lichenoid pattern
  - Epidermal alterations are variable and include parakeratosis, slight acanthosis, spongiosis, exocytosis, and basal layer vacuolization
  - Extravasated red blood cells (RBCs) and often subtle hemosiderin deposits are found in vicinity of capillaries
    - Vascular injury is usually minimal
    - However, one can observe deposition of fibrinoid material in vessel walls, particularly in Gougerot-Blum disease or eczematoid-like purpura of Doucas and Kapetanakis
  - Older lesions show less dense infiltrate and capillaries often show dilatation of their lumen and proliferation of their endothelium
    - Extravasated RBCs may no longer be present, but one frequently finds hemosiderin deposition: Iron stain useful in these cases
  - In eczematid-like purpura of Doucas and Kapetanakis, there is spongiosis and parakeratosis is more prominent
  - Granulomatous variant shows superficial, nonnecrotizing granulomatous infiltrate, with extravasation of erythrocytes and hemosiderin deposition

## ANCILLARY TESTS

### Genetic Testing

- Almost 50% of PPDs are monoclonal

## DIFFERENTIAL DIAGNOSIS

### Stasis Dermatitis

- Usually is much deeper into the dermis
- More pronounced epidermal changes and fibrosis of dermis

### Atypical T-Cell Process

- Careful evaluation for epidermotropism, lymphoid atypia, and clinicopathologic correlation is necessary
- T-cell clonality studies less helpful

### Lichenoid Dermatitis or Lichenoid Drug Reaction

- Abundant Civatte bodies or basal layer vacuolation

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## KEY FACTS

### CLINICAL ISSUES

- Anogenital region most common, but extragenital lesions are not rare
- Ivory white to light pink plaques, sharply demarcated
- Lesions may show atrophy &/or cigarette paper-like surface
- Other tumors may develop in anogenital lesions, particularly squamous cell carcinoma

### MICROSCOPIC

- Early lesions
  - Lichenoid infiltrate of lymphocytes
- Well-developed lesions
  - Vacuolar change in basal cells, zone of hyalinization, &/or edema in superficial dermis

### TOP DIFFERENTIAL DIAGNOSES

- Lichen planus
  - Lichenoid infiltrate of lymphocytes abutting and obscuring dermoepidermal junction

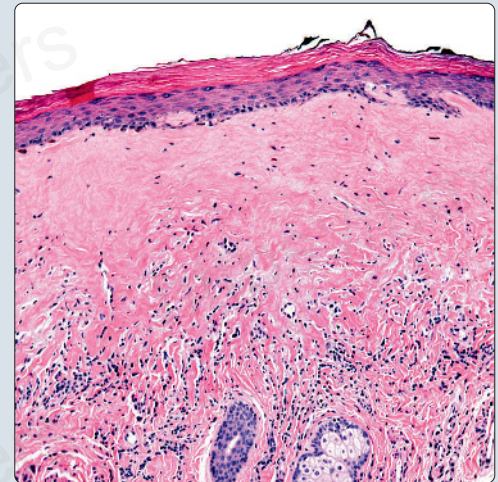
- Civatte/colloid bodies
- No zone of hyalinization
- Acanthosis
- Clinically violaceous to pink papules and plaques
- Mycosis fungoides
  - Early lesions of lichen sclerosis, when lymphocytes tag dermoepidermal junction, may mimic mycosis fungoides
  - Clinicopathologic correlation necessary
- Morphea
  - Overlaps with extragenital lichen sclerosis
  - Lesions of morphea generally do not show cigarette paper atrophy of skin
  - Dermal sclerosis with thickened collagen bundles generally involving entire reticular dermis
  - No thickened basement membrane or vacuolar alteration
  - Retained elastic fibers

### Atrophic, Wrinkled Skin

**(Left)** Extragenital lichen sclerosis on the thigh is shown here. There is typical atrophy manifested by fine wrinkling of the skin surface. The lesion is subtly lighter in color than normal skin. **(Right)** In lichen sclerosis, there is hyperkeratosis with basilar vacuolar change. There is dermal hyalinization with an inferiorly displaced perivascular/band-like infiltrate of lymphocytes.

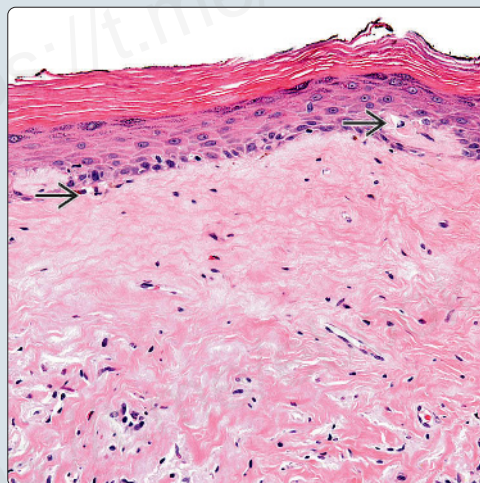


### Papillary Dermal Sclerosis

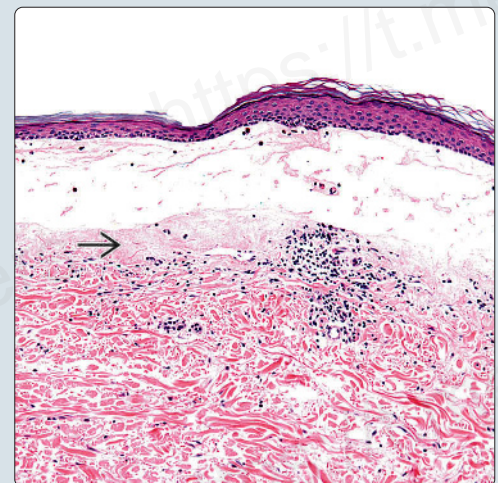


### Vacuolar Alteration

**(Left)** In lichen sclerosis, there is typically hyperkeratosis with vacuolar change at the base of the epidermis. In well-developed lesions, there is prominent hyalinization of the superficial dermis. **(Right)** In this example of lichen sclerosis, prominent dermal edema separates the epidermis and dermis. Below the cleft, there is hyalinization and perivascular inflammation.



### Edema of Papillary Dermis



## TERMINOLOGY

### Synonyms

- Lichen sclerosus
- Balanitis xerotica obliterans

### Definitions

- Chronic dermatosis, generally affecting anogenital region

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- In Europe only, *Borrelia burgdorferi* has been detected in lesional skin, possibly because predominant strains in Europe are *B. garinii* and *B. afzelii*

## CLINICAL ISSUES

### Epidemiology

- Sex
  - More common in women

### Site

- Anogenital region most commonly
- Extragenital lesions
  - May be evident in absence of anogenital lesions
  - May show clinical/histopathologic overlap with morphea

### Presentation

- Symptoms/signs
  - Lesions variably pruritic &/or painful
  - Dyspareunia may be present
  - Phimosis may complicate lesions in males
- Ivory white to light pink plaques, sharply demarcated
- Lesions may show atrophy &/or cigarette paper-like surface
- Follicular plugging, telangiectasias, &/or purpura may be evident
- Rarely, bullae form
- Lesions may be linear or Blaschkoid
- Malignant transformation may complicate long-standing anogenital lesions
  - Squamous cell carcinoma
  - Melanocytic lesions
  - Verruciform xanthoma

### Laboratory Tests

- Up to 70% of patients may have circulating autoantibodies to extracellular matrix protein 1 (ECM1)

### Treatment

- Drugs
  - High-potency topical corticosteroids often effective

## MICROSCOPIC

### Histologic Features

- Early lesions
  - Lichenoid infiltrate of lymphocytes
- Well-developed lesions
  - Vacuolar change in basal cells
  - Thickened basement membrane
  - Zone of hyalinization &/or edema in superficial dermis, with homogenization of papillary dermal collagen

- Hyalinized zone contains dilated vessels and extravasated erythrocytes
- Inflammatory cells (particularly lymphocytes) around vessels or in band below hyalinized zone
- In all lesions, variable hyperkeratosis
- Epidermis may be atrophic but is sometimes acanthotic
- Sometimes follicular ostia are plugged by hyperkeratosis

## ANCILLARY TESTS

### Histochemistry

- Elastic van Gieson
  - Shows decreased elastic fibers in zone of hyalinization

### Genetic Testing

- Occasional cases show T-cell clonality

## DIFFERENTIAL DIAGNOSIS

### Lichen Planus

- Clinical
  - Violaceous to pink papules and plaques
- Histopathologic
  - Lichenoid infiltrate of lymphocytes abutting and obscuring dermo-epidermal junction
  - Civatte/colloid bodies
  - Hyperkeratosis and wedge-shaped hypergranulosis
  - Acanthosis
  - No zone of hyalinization

### Mycosis Fungoides

- Early lesions of lichen sclerosus, when lymphocytes tag dermoepidermal junction, may mimic mycosis fungoides
- Clinicopathologic correlation necessary

### Morphea

- Clinical
  - Overlaps with extragenital lichen sclerosus
  - Lesions of morphea generally do not show cigarette paper-like atrophy of skin
- Histopathologic
  - Dermal sclerosis with thickened collagen bundles generally involving entire reticular dermis
  - No thickened basement membrane or vacuolar alteration
  - Perieccrine and perineural inflammation with plasma cells may be evident
  - Retained elastic fibers

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## KEY FACTS

### TERMINOLOGY

- Multisystem disease affecting skin and gastrointestinal tract occurring in immunosuppressed transplant recipients
- Occurs as result of immunocompetent donor T lymphocytes responding to incompatible foreign host major histocompatibility complex antigens

### CLINICAL ISSUES

- Most commonly occurs in allogenic bone marrow transplants

### MICROSCOPIC

- Acute graft-vs.-host disease (GVHD)
  - Focal or diffuse interface dermatitis with scattered apoptotic keratinocytes closely associated with neighboring lymphocytes (satellite cell necrosis)
- Chronic lichenoid GVHD

- Parakeratosis, hypergranulosis, and irregular acanthosis with dense dermal lichenoid infiltrate leading to vacuolar interface change with cytotid body formation
- Chronic sclerodermoid GVHD
  - Epidermal atrophy with flattening of rete ridge pattern and marked dermal fibrosis leading to loss of adnexal structures
- In either chronic form, other characteristic features of GVHD (including vacuolar interface change, satellite cell necrosis, and perivascular infiltrate) are variably present

### TOP DIFFERENTIAL DIAGNOSES

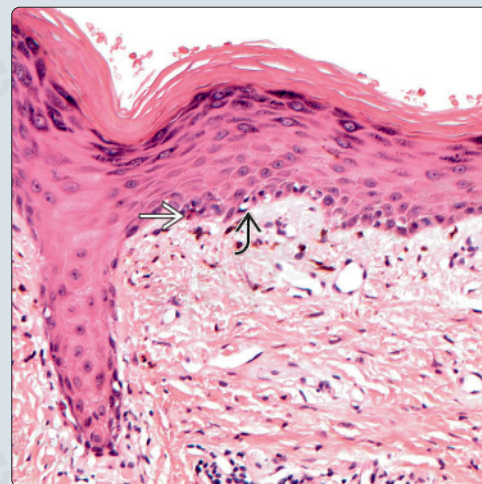
- Drug reaction
- Erythema multiforme
- Toxic epidermal necrolysis
- Viral exanthem
- Eruption of lymphocyte recovery

### Acute Graft-vs.-Host Disease

(Left) Clinical photo of acute graft-vs.-host disease (GVHD) shows ill-defined violaceous papules & macules with overlying scale. This was in a generalized morbilliform distribution. (Courtesy S. Worswick, MD.) (Right) Grade I acute GVHD shows sparse interface changes with few apoptotic keratinocytes and closely associated lymphocytes (satellite cell necrosis).

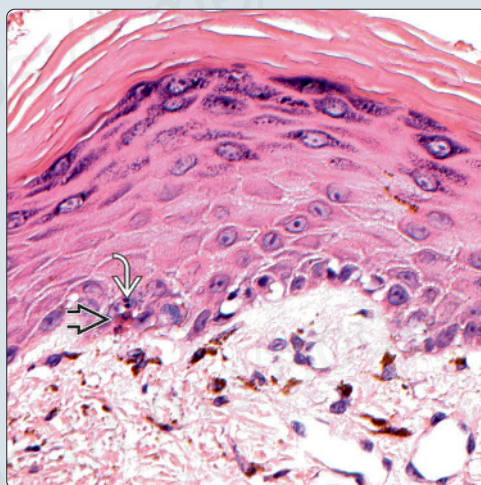


### Grade I Acute GVHD

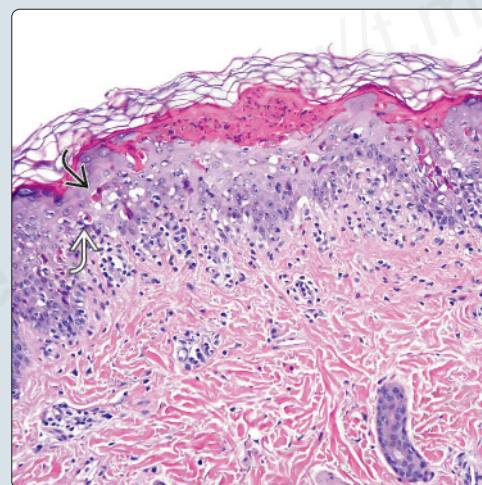


### Satellite Cell Necrosis

(Left) Grade I acute GVHD shows satellite cell necrosis, characterized by apoptotic keratinocytes with intensely eosinophilic appearance and an adjacent lymphocyte. (Right) Grade II acute GVHD shows more extensive interface changes along with satellite cell necrosis characterized by apoptotic keratinocytes with adjacent lymphocytes.



### Grade II Acute GVHD



## TERMINOLOGY

### Abbreviations

- Graft-vs.-host disease (GVHD)

### Definitions

- Multisystem disease affecting skin and gastrointestinal tract, occurring in immunosuppressed transplant recipients
- Occurs as result of immunocompetent donor T lymphocytes responding to incompatible foreign host major histocompatibility complex antigens
- Acute GVHD
  - Classically occurs within 100 days of transplant with peak incidence around day 30
- Chronic GVHD
  - Typically occurs within 3-5 months after grafting and primarily consists of either lichen planus-like eruption or scleroderoid form

## ETIOLOGY/PATHOGENESIS

### Proposed Immunologic Mechanisms

- Donor T lymphocytes activate and proliferate in setting of immunocompromised host because host cannot reject transplanted cells
- Pretransplant tissue damage, through radiation or chemotherapy, is thought to increase recognition of host's antigens by donor's T lymphocytes
- Donor T lymphocytes cause host cell death through cytotoxic T-cell effects mediated by perforin, granzyme, and apoptosis through Fas/Fas ligand pathway
- Occurrence related to HLA mismatch, but minority of cases develop due to mismatch of minor histocompatibility antigens

## CLINICAL ISSUES

### Presentation

- Most commonly occurs in allogeneic bone marrow transplants but also reported in
  - Solid organ transplantation, severely immunosuppressed patients following transfusion of nonirradiated blood products, transplacentally to immunodeficient fetus, and rarely in autologous transplants
- Acute GVHD
  - Initially, morbilliform rash characterized by erythematous macules & papules with possible mucosal involvement
  - Begins with punctate lesions around adnexal structures involving face, trunk, palms, & soles
  - Can also present as acral erythema, eczema-like eruption, ichthyosis, or, in severe cases, erythroderma with diffuse desquamation mimicking toxic epidermal necrolysis
  - Other clinical features include cholestatic hepatitis with increased bilirubin and high-volume diarrhea
- Chronic GVHD
  - Lichenoid chronic GVHD
    - May present with malar rash and lichen planus-like eruption characterized by brownish to purple flat-topped papules, occurring initially on distal extremities before becoming generalized
    - With chronicity, skin can become poikilodermatous with atrophy, telangiectasia, and dyspigmentation

- Scleroderoid chronic GVHD
  - Morphea-like lesions may occur as atrophic shiny plaques with overlying cigarette paper atrophy of skin located in areas of pressure
  - Changes can also involve oral or genital mucosa and nails
  - Deep sclerotic lesions may also occur, resulting in contractures and limited mobility

### Treatment

- Drugs
  - High-dose systemic corticosteroids are effective in some patients but often are inadequate for higher grade GVHD
  - Rituximab is used in chronic GVHD, both lichenoid and scleroderoid variants
  - Skin targeted topical corticosteroids &/or topical tacrolimus 0.1%
- Radiation
  - Extracorporeal photophoresis or narrow band ultraviolet B phototherapy in refractory acute and chronic GVHD patients; ultraviolet A phototherapy in patients with chronic GVHD

### Prognosis

- Acute GVHD has high mortality, but in patients who survive, rash will either completely resolve or persist to become chronic GVHD
- Chronic GVHD is often unremitting disease with variable course of progression and 5-yr survival rate of ~ 40-50% in patients with progressive disease

## MICROSCOPIC

### Histologic Features

- Acute GVHD
  - Focal or diffuse interface dermatitis with scattered apoptotic keratinocytes in all levels of epidermis that are closely associated with neighboring lymphocytes (satellite cell necrosis)
  - Mild perivascular chronic inflammatory cell infiltrate with telangiectatic blood vessels and endothelial swelling
  - In established lesions, accompanying parakeratosis with more extensive keratinocyte apoptosis
  - Microvesiculation can occur at dermal-epidermal junction (DEJ)
  - Interface changes typically also involve hair follicles (hair bulge particularly affected) and eccrine glands
  - Exocytosis of lymphocytes and occasional epidermal spongiosis
- Chronic lichenoid GVHD
  - Parakeratotic hyperkeratosis, hypergranulosis, and irregular acanthosis with vacuolar interface change at DEJ and cytoid bodies
  - Dense lichenoid inflammation with obscuring of DEJ
- Chronic scleroderoid GVHD
  - Epidermal atrophy with flattening of rete ridge pattern and marked dermal fibrosis leading to loss of adnexal structures
  - Other characteristic features of GVHD variably present
    - Vacuolar interface change, satellite cell necrosis, and perivascular infiltrate

**Grading of Acute GVHD**

- Grade I: Focal or diffuse vacuolar change at dermal-epidermal junction
- Grade II: In addition to vacuolar alteration at DEJ, accompanying epidermal spongiosis with apoptotic keratinocytes
- Grade III: Features found in grades I and II, plus subepidermal clefting, more spongiosis, and more dyskeratotic keratinocytes
- Grade IV: Complete epidermal detachment with extensive epidermal necrosis

**ANCILLARY TESTS****In Situ Hybridization**

- Fluorescent labeling in biopsy specimens to identify known mismatched donor lymphocytes present in interface inflammation

**DIFFERENTIAL DIAGNOSIS****Histopathologic**

- Acute
  - Drug reaction
    - Histology: Often indistinguishable from acute GVHD, although tends to have more conspicuous eosinophils
    - Some feel very high number of eosinophils (average > 16/10 HPF) is required to rule out GVHD
  - Viral exanthem
    - Can be challenging as it is difficult to distinguish between acute GVHD and viral eruptions
  - Eruption of lymphocyte recovery
    - Mild spongiosis with lymphocyte exocytosis and mild interface changes with keratinocyte atypia due to chemotherapy effect with minimal dyskeratosis
    - Can be indistinguishable from grades I or II acute GVHD with dyskeratotic keratinocytes and satellite cell necrosis
  - Erythema multiforme
    - Lymphocyte-predominant superficial infiltrate with apoptotic keratinocytes, although not classic satellite cell necrosis with acute GVHD
    - Can be difficult to distinguish on pathologic grounds alone
  - Toxic epidermal necrolysis
    - Mild superficial perivascular inflammation, often with subepidermal split and full thickness necrosis of overlying epidermis
    - Grade IV GVHD can be difficult to distinguish because there is complete loss of epidermis
- Chronic lichenoid
  - Lichen planus
    - In developed lesions, dense lichenoid inflammation with obscuring of DEJ that becomes squamitized and develops saw tooth pattern
    - Necrotic epidermal keratinocytes (Civatte bodies) and superficial dermal necrotic keratinocytes (colloid bodies)
    - Overlying wedge-shaped hypergranulosis and orthokeratosis
  - Lichenoid chronic GVHD may have similar histopathologic appearance, but has less inflammation, and satellite cell necrosis is more characteristically seen in GVHD
- Chronic scleroderroid
  - Systemic sclerosis
    - Acute phase: Perivascular lymphocyte-predominant infiltrate containing plasma cells at dermal subcutaneous junction with overlying dermal sclerosis and loss of adnexal fat
    - Advanced stages: Inflammation usually lacking and entire biopsy shows dermal sclerosis with loss of adnexal structures
    - Late chronic GVHD can have same appearance as late systemic sclerosis and would need to be distinguished on clinical grounds

**Clinical**

- Acute
  - Drug reaction
    - Most commonly presents as generalized morbilliform exanthem that tends to lack facial and palmar involvement seen in acute GVHD
  - Viral exanthem
    - Like drug eruption, appears as generalized morbilliform eruption
  - Eruption of lymphocyte recovery
    - Results from return of lymphocytes into circulation after chemotherapy and usually occurs within 2 weeks after transplant
    - Clinical symptoms include fever, acral erythema and edema, and generalized morbilliform eruption with pulmonary edema
    - Often, timing of eruption of lymphocyte recovery is earlier than when acute GVHD occurs, although rare hyperacute form of GVHD can occur in this time frame
  - Erythema multiforme
    - Presents as targetoid macules with involvement of palms and soles and possible mild involvement of oral mucosa
    - Often associated with herpesvirus infection
  - Toxic epidermal necrolysis
    - Severe cutaneous reaction (often to medications) that presents as diffuse epidermal necrosis and sloughing with mucous membrane involvement
- Chronic lichenoid
  - Lichen planus
    - Localized or generalized purple, pruritic, polygonal papules with overlying lacy white reticulation; can be best appreciated when lesions involve mucosal surfaces

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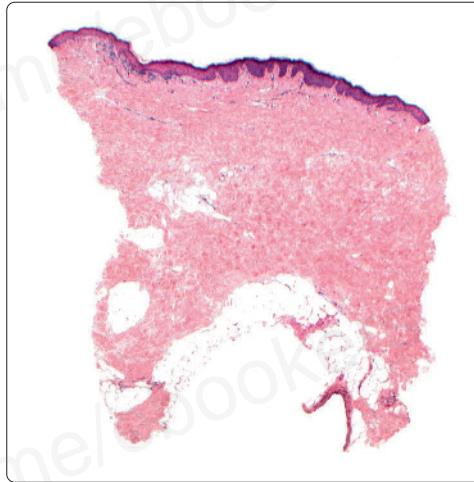
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**Chronic Sclerodermoid GVHD**

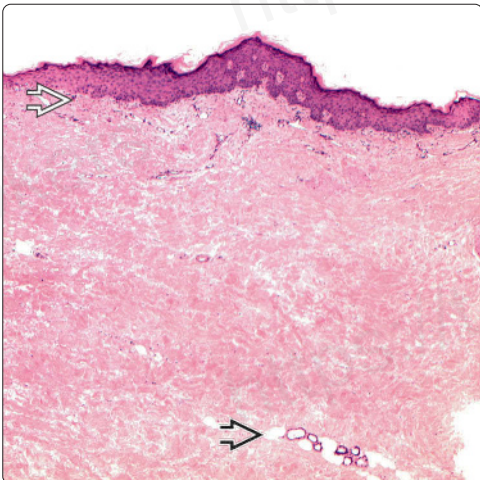


**Squared Off**

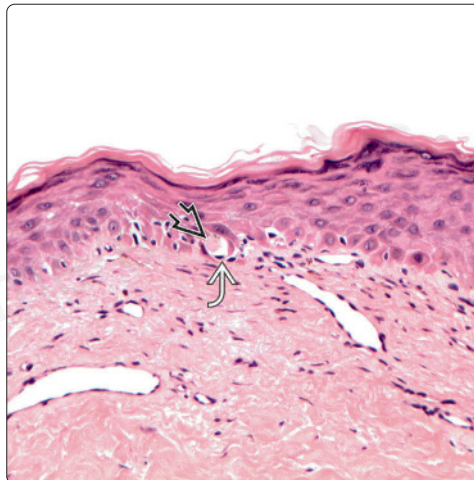


(Left) Chronic sclerodermoid GVHD shows dyspigmented scar-like plaques with epidermal atrophy and telangiectasias. Also note the dystrophic nail changes. (Courtesy N. Gharavi, MD.) (Right) Chronic sclerodermoid GVHD on scanning magnification demonstrates a squared-off appearance due to the sclerosis of dermal collagen. Decreased adnexal structures are also noted. Late stage morphea/scleroderma can have an almost identical appearance.

**Loss of Epidermis and Adnexae**

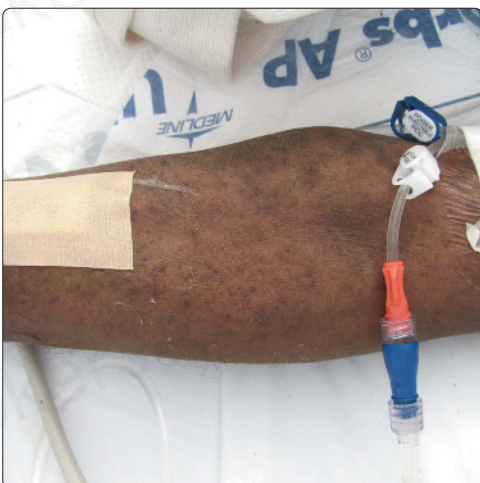


**Subtle Interface Changes**

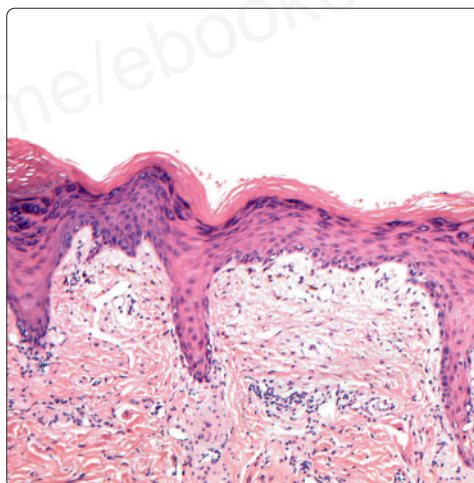


(Left) Chronic sclerodermoid GVHD shows atrophy of the epidermis with loss of the typical rete ridge pattern. Note the thick sclerotic dermal collagen and decreased eccrine subcutaneous fat. (Right) Chronic sclerodermoid GVHD still demonstrates subtle features of GVHD with interface change and an apoptotic keratinocyte with an adjacent lymphocyte (satellite cell necrosis).

**Acute GVHD**



**Grade I Acute GVHD**



(Left) Acute GVHD is characterized by generalized macules and papules (morbilliform eruption). (Courtesy S. Worswick, MD.) (Right) Grade I acute GVHD (10x, H&E) shows sparse perivascular and lichenoid lymphocytic inflammation with focal skip areas of interface change and apoptotic keratinocytes. Grade I GVHD characterized by interface changes with few apoptotic keratinocytes.



## KEY FACTS

### TERMINOLOGY

- Pityriasis lichenoides et varioliformis acuta (PLEVA)
  - Mucha-Habermann disease, febrile ulceronecrotic Mucha-Habermann disease
  - Recurrent crops of erythematous papules of unknown etiology favoring children or young adults and spontaneously resolving over weeks
- Pityriasis lichenoides chronica (PLC)
  - Guttate parapsoriasis
  - Chronic form of PLEVA also typically affecting children but can affect any age; predominantly truncal rash persists for years

### MICROSCOPIC

- PLEVA
  - Superficial perivascular brisk lymphocytic infiltrate with interface change at dermal-epidermal junction; infiltrate extends into reticular dermis in wedge-shaped fashion

- Epidermis with dyskeratosis, crust, foci of parakeratosis, acanthosis, and basal layer vacuolar change
- Eosinophils are not typically seen
- PLC
  - Blunted features of PLEVA seen
  - Parakeratosis with less lymphocytic infiltrate in dermis and less interface change at dermal-epidermal junction with focal apoptotic keratinocytes
  - No atypical lymphocytes in either entity
  - Eosinophils are not typically seen

### TOP DIFFERENTIAL DIAGNOSES

- Lymphomatoid papulosis
- Drug eruption
- Arthropod reactions
- Guttate psoriasis
- Pityriasis rosea

**Crusted Necrotic Erythematous Papules on Trunk**

(Left) *Pityriasis lichenoides et varioliformis acuta (PLEVA)* consists of scattered crusted necrotic erythematous papules located on the trunk and extremities. (Courtesy K. Suh, MD.) (Right) PLEVA classically shows scattered truncal and extremity edematous and crusted papules. (Courtesy K. Suh, MD.)



**Crusted Papules of PLEVA**

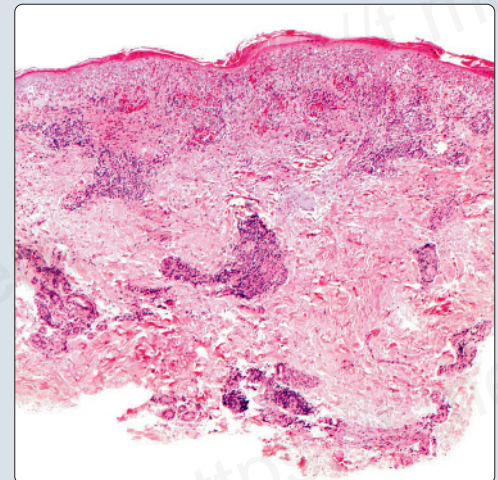


**Ulcerated Papule**

(Left) Close-up view shows a necrotic and ulcerated lesion in a patient with PLEVA. (Courtesy K. Suh, MD.) (Right) PLEVA at low power demonstrates a wedge-shaped lymphocytic infiltrate extending to the deep papillary dermis along with the obscured dermal-epidermal junction due to interface change.



**Wedge-Shaped Lymphocytic Inflammation**



## TERMINOLOGY

### Synonyms

- Pityriasis lichenoides et varioliformis acuta (PLEVA), Mucha-Habermann disease, febrile ulceronecrotic Mucha-Habermann disease
- Pityriasis lichenoides chronica (PLC), guttate parapsoriasis

## ETIOLOGY/PATHOGENESIS

### Unknown

- Proposed hypersensitivity reaction to viruses, possible autoimmune association (rheumatoid arthritis, hypothyroidism, pernicious anemia), or drug induced

## CLINICAL ISSUES

### Presentation

- PLEVA
  - More common in children, with male predominance; asymptomatic recurrent crops of crusted erythematous papules or vesicles that self resolve over period of weeks
    - May heal with scarring, resembling variola
  - In acute febrile ulceronecrotic variant, constitutional symptoms such as fever, malaise, arthritis, and lymphadenopathy are also present
  - Those with diffuse skin lesions appear to have shorter course than patients with peripheral skin lesions
- PLC
  - Any age group can be affected but often seen in children as red brown papules with characteristic scale that slowly regress over months
  - Can take on chronic relapsing course with prolonged periods of remission in between flares

### Treatment

- 1st line with topical corticosteroids, topical coal tar, phototherapy, antihistamines, or oral tetracycline or erythromycin for antiinflammatory effects
- Treat systemic symptoms with systemic corticosteroids and refractory cases with weekly methotrexate

### Prognosis

- PLEVA: Self-resolving over weeks
- Acute febrile ulceronecrotic PLEVA: Usually lasts several months with relapsing disease and eventually converts into classic PLEVA; rare reports of death typically in adult cases
- PLC: Chronic relapsing course over months with eventual tendency for self resolution, though rare cases of progression to cutaneous T-cell lymphoma have been reported

## MICROSCOPIC

### Histologic Features

- PLEVA
  - Superficial perivascular brisk lymphocytic infiltrate with lichenoid interface change at dermal-epidermal junction; infiltrate extends into reticular dermis in wedge-shaped fashion
  - Prominent lymphocyte exocytosis with intraepidermal individually necrotic keratinocytes

- Epidermis with overlying crust, foci of parakeratosis, acanthosis, and basal layer vacuolar change
  - May see neutrophils in parakeratotic stratum corneum
- Depending on extent of infiltrate, edema, and epidermal necrosis may also be present along with extravasation of red blood cells and lymphocytic vasculopathy
- Eosinophils are not typically seen
- PLC
  - Blunted features of PLEVA are seen
  - Parakeratosis with less lymphocytic infiltrate in dermis and less interface change at dermal-epidermal junction with focal apoptotic keratinocytes
  - Perivascular lymphocytic inflammation in superficial dermis ± extravasation of red blood cells
  - No atypical lymphocytes in either PLEVA or PLC
  - Eosinophils are not typically seen

## DIFFERENTIAL DIAGNOSIS

### Lymphomatoid Papulosis

- Self-healing benign eruption with malignant-appearing histology
- Dense atypical lymphocytic infiltrate distributed in wedge-shaped, lichenoid pattern or large cell variant often with overlying crust and necrotic keratinocytes
- Frequently CD30(+)

### Drug Eruption

- Superficial perivascular dermal lymphohistiocytic infiltrate with conspicuous eosinophils distinguishing this entity from PLEVA
- Interface change typically more vacuolar than lichenoid

### Arthropod Reactions

- Histologic spectrum, but classically wedge-shaped mixed dermal infiltrate with eosinophils, overlying epidermal spongiosis, crust, and occasional identifiable insect mouth parts

### Guttate Psoriasis

- Eruptive small, scattered, oval papules and plaques with overlying scale occurring in younger patients
- Multiple discrete mounds of parakeratosis with collections of neutrophils overlying hypogranulosis and slight acanthosis; superficial perivascular infiltrate and dilated superficial vessels
  - Neutrophils are seen at top of mounds of parakeratosis

### Pityriasis Rosea

- Diffuse truncal, self-resolving, salmon-colored, oval papules with scale often preceded by herald patch or larger single scaly plaque
- Nonspecific histologic features with slight psoriasiform hyperplasia, focal hyperkeratosis, and parakeratosis overlying superficial perivascular infiltrate with extravasation of red blood cells

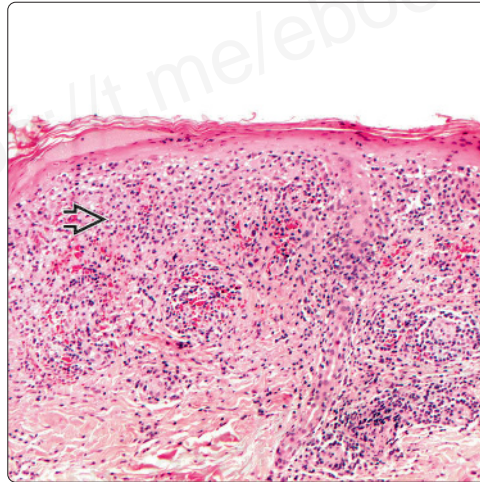
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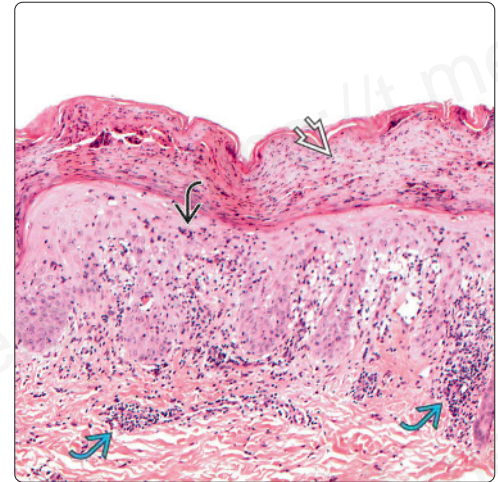


**Lichenoid Interface Change**

(Left) PLEVA shows a brisk lymphocytic infiltrate in the papillary dermis with interface changes noted by loss of a clear dermal-epidermal junction with vacuolization or clear spaces around basal layer keratinocytes. (Right) PLEVA shows a thick parakeratotic crust overlying an acanthotic epidermis with brisk lymphocytic inflammation, interface change, and exocytosis.

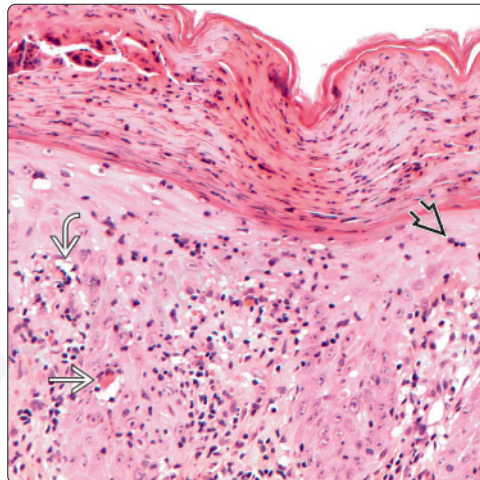


**Parakeratotic Crust**

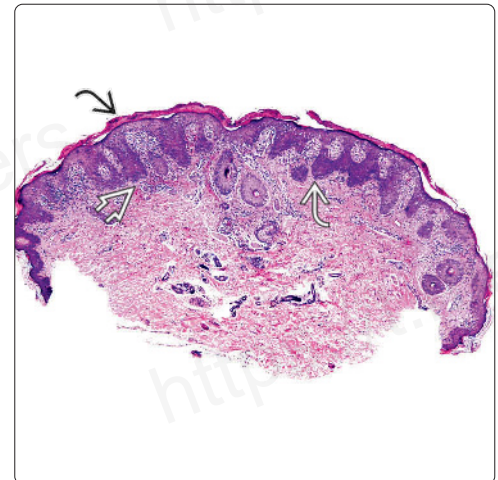


**Dyskeratosis in PLEVA**

(Left) PLEVA at a higher power demonstrates significant basal layer vacuolar change with numerous necrotic keratinocytes, exocytosis of typical lymphocytes, and extravasated red blood cells in the superficial dermis. (Right) Pityriasis lichenoides chronica (PLC) shows blunted features of PLEVA such as a mild lichenoid infiltrate extending into the superficial reticular dermis. Features of chronicity that can be appreciated are hyperkeratosis and acanthosis.

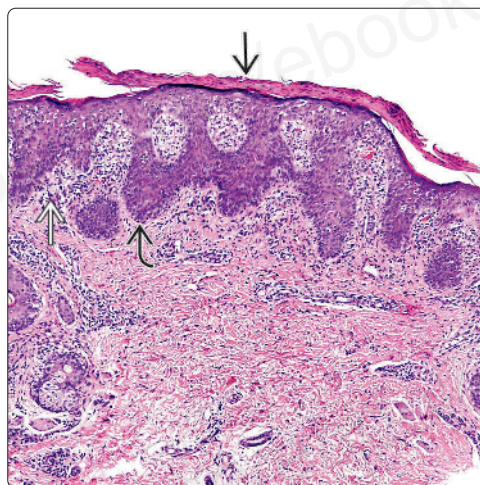


**Lichenoid Infiltrate in PLC**

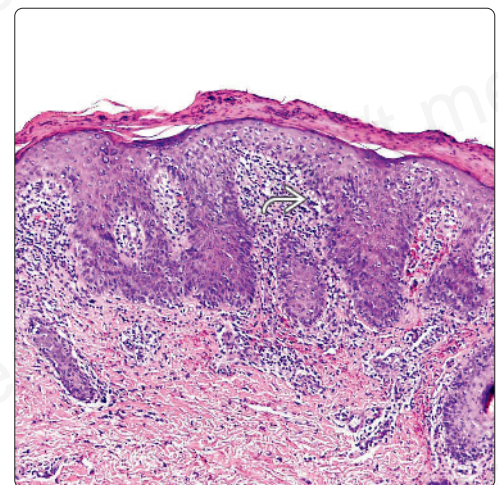


**Parakeratosis in PLC**

(Left) PLC shows parakeratosis overlying an acanthotic epidermis with mild superficial lichenoid infiltrate and interface change. (Right) PLC has focal areas of basal layer interface change, as opposed to interface change occurring over a broad front like in PLEVA.



**Focal Vacuolar Alteration**

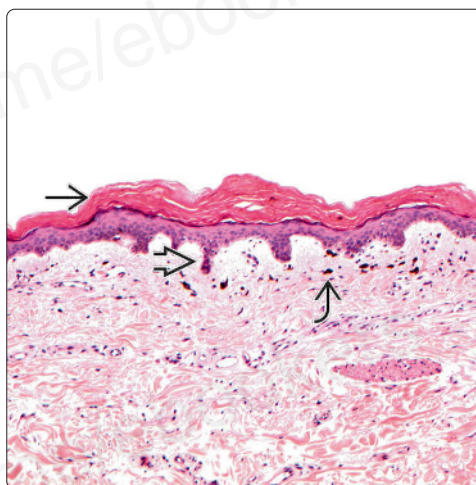




**Symmetric Papulosquamous Eruption of PLC**

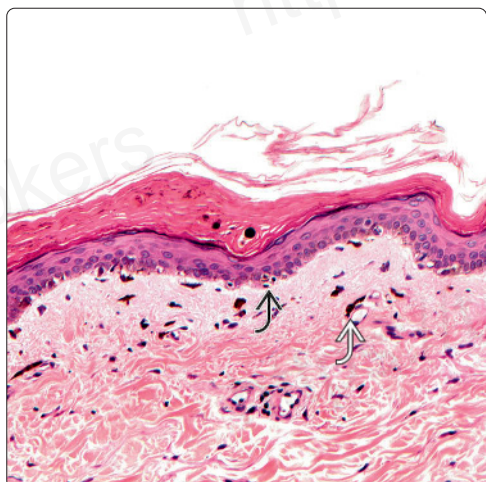


**Chronic Changes**

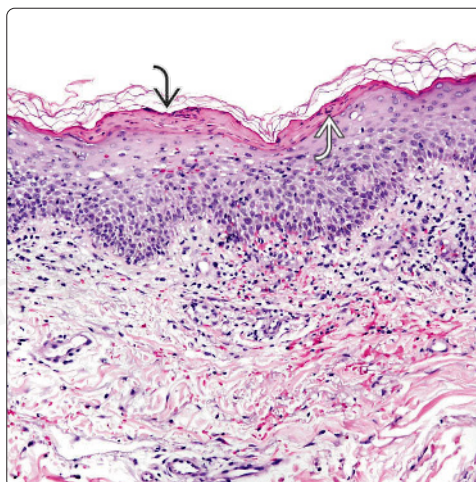


(Left) PLC presented in this patient over the abdomen with symmetric, pink, papulosquamous eruption without evidence of excoriations. Biopsy was diagnostic. (Right) PLC demonstrates hyperkeratosis overlying a slightly acanthotic epidermis with sparse superficial perivascular lymphocytic inflammation containing melanophages in the superficial dermis, which can signify interface change.

**Basilar Vacuolar Change**

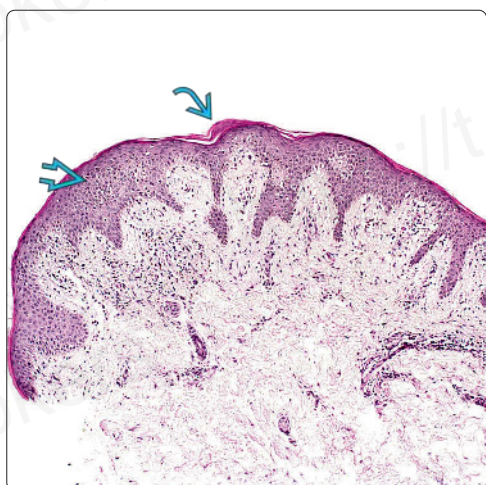


**Guttate Psoriasis**

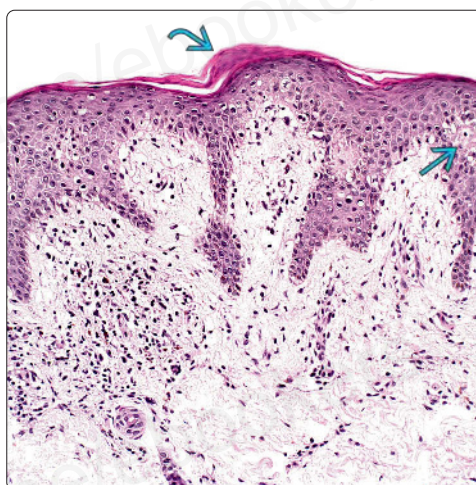


(Left) PLC shows light basal layer vacuolar change with papillary dermal pigment incontinence. Notice how the histologic changes are more subtle in PLC compared to PLEVA. (Right) Guttate psoriasis can appear similar, but note the discrete mounds of parakeratosis with occasional neutrophils overlying hypogranulosis and slight acanthosis. There is also a superficial perivascular infiltrate and dilated superficial vessels.

**Pityriasis Rosea With Mounds of Parakeratosis**



**Foci of Spongiosis in Pityriasis Rosea**



(Left) Although pityriasis rosea may appear similar at low power, there is no vacuolar alteration and there are mounds of parakeratosis with associated spongiosis. (Right) Although nonspecific, pityriasis rosea is characterized by a gently undulating epidermis with mounds of parakeratosis and foci of spongiosis usually near the foci of parakeratosis.



## KEY FACTS

### TERMINOLOGY

- Papulosquamous condition, often begins on face/scalp and extends caudally

### ETIOLOGY/PATHOGENESIS

- Majority of cases sporadic

### CLINICAL ISSUES

- Classical presentation
  - Papules/plaques with orange hue
  - Follicular prominence, especially over dorsal fingers
  - Palmoplantar keratoderma
- If erythroderma is present, generally islands of normal skin ("islands of sparing") are evident
- In adults, disease may run its course over 1-5 years

### MICROSCOPIC

- Hyperkeratosis and parakeratosis
  - Alternating in checkerboard pattern

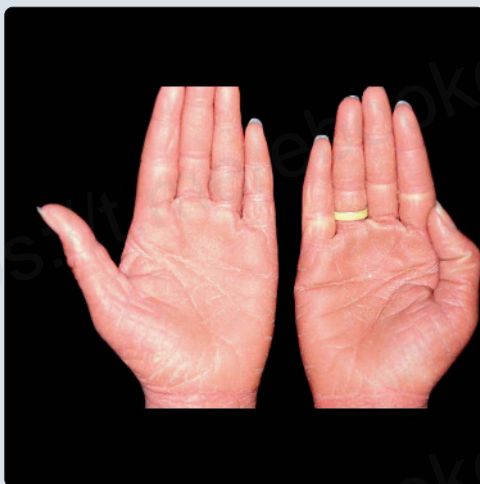
- Irregular acanthosis
- Acantholysis may be evident
  - May serve as histopathologic clue to diagnosis before erythroderma ensues
- Superficial perivascular lymphocytic infiltrate
- Follicular plugging

### TOP DIFFERENTIAL DIAGNOSES

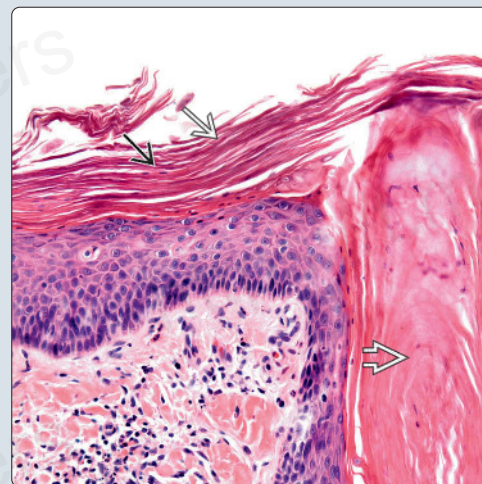
- Psoriasis
  - Often confluent parakeratosis
  - Neutrophils in stratum corneum
  - Regular acanthosis, hypogranulosis
- Sézary syndrome
  - Flow cytometry often necessary to make diagnosis
- Dermatomyositis
  - Subtle interface vacuolar changes with occasional necrotic keratinocytes, sparse inflammation

Orange Waxy Keratoderma of PRP

(Left) In typical pityriasis rubra pilaris, there is often a characteristic orange-hued waxy keratoderma of the palms &/or soles. (Courtesy S. Vanderhooft, MD.) (Right) Pityriasis rubra pilaris often shows a checkerboard pattern of alternating parakeratosis and orthokeratosis in the stratum corneum. There is typically follicular plugging.

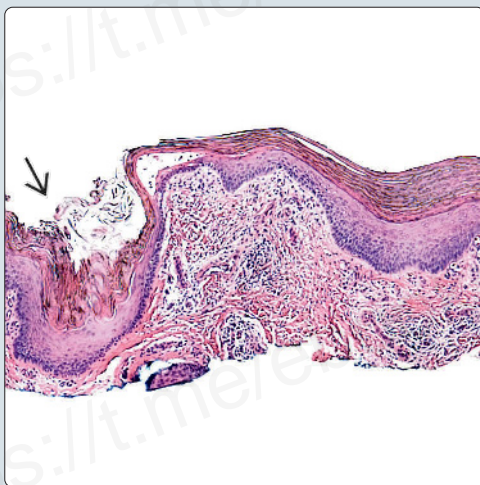


Alternating Parakeratosis and Orthokeratosis

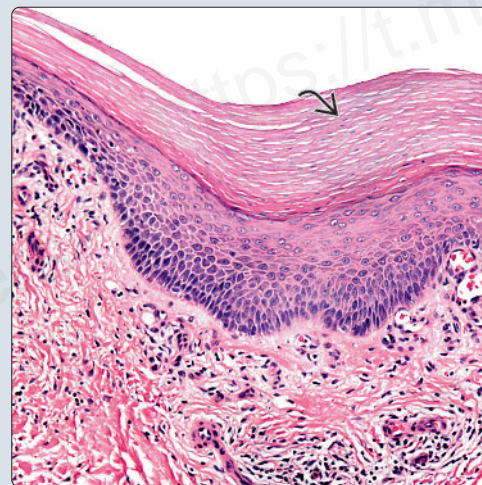


Follicular Plugging and Irregular Acanthosis

(Left) Pityriasis rubra pilaris characteristically shows follicular plugging and irregular acanthosis with hyperkeratosis. A perivascular lymphocytic infiltrate is also present. (Right) In this example of pityriasis rubra pilaris, there is nonspecific hyperkeratosis with some parakeratosis and irregular acanthosis.



Hyperkeratosis With Irregular Acanthosis





## TERMINOLOGY

### Abbreviations

- Pityriasis rubra pilaris (PRP)

### Definitions

- Papulosquamous condition; often begins on face/scalp and extends caudally
- Often orange hue to lesions, follicular prominence, palmoplantar hyperkeratosis
- If erythroderma is present, generally islands of normal skin ("islands of sparing") are evident

## ETIOLOGY/PATHOGENESIS

### Unknown, With Associations

- Majority of cases sporadic
- Rarely associated with HIV infection
- Rarely associated with internal malignancy (paraneoplastic PRP)
- Rarely familial
  - Associated with *CARD* gene mutations
- Rarely drug-related or associated with infection

## CLINICAL ISSUES

### Epidemiology

- Age
  - Bimodal distribution: 1st and 5th decades

### Presentation

- Classical presentation
  - Begins on face/scalp, extends caudally over several weeks to months with islands of normal skin
  - Papules/plaques
    - Orange-red with dry scale
  - Follicular prominence, especially over dorsal fingers
  - Palmoplantar keratoderma
  - Dystrophic nails
  - In erythrodermic patients, ectropion may be seen
- Photodistribution or photoexacerbation may be evident
- Variable pruritus
- Atypical presentations
  - Localized lesions to elbows/knees/thigh

### Natural History

- In adults, disease may run its course over 1-5 years
- Recurrence possible

### Treatment

- Drugs
  - Localized disease
    - Topical therapy (e.g., with steroids or retinoids or vitamin D analogues)
  - Widespread disease
    - Oral therapy (e.g., with methotrexate or retinoids)
  - Refractory disease
    - TNF- $\alpha$  inhibitors have been used in isolated cases

### Griffiths Classification

- Type I: Classic adult type
- Type II: Atypical adult type
- Type III: Classic juvenile type

- Type IV: Circumscribed juvenile type
- Type V: Atypical juvenile type
- Type VI: HIV associated

## MICROSCOPIC

### Histologic Features

- Hyperkeratosis and parakeratosis
  - Alternating in checkerboard pattern
- Irregular acanthosis
  - Broad rete ridges
  - Thick suprapapillary plates
  - Retained granular layer
- Acantholysis (various patterns) may be evident
  - Pemphigus-like, Darier-like, and Hailey-Hailey-like
  - May serve as histopathologic clue to diagnosis before erythroderma ensues
- Rarely epidermolytic hyperkeratosis is evident
- Superficial perivascular lymphocytic infiltrate
  - Occasionally may be lichenoid
  - Eosinophils may be intermixed
- Follicular plugging

## DIFFERENTIAL DIAGNOSIS

### Psoriasis

- Clinical
  - If erythrodermic
    - Often preceding history of plaque psoriasis
- Histopathologic findings
  - Often confluent parakeratosis
  - Neutrophils in stratum corneum
  - Regular acanthosis, hypogranulosis
  - Increased suprabasilar mitoses
  - Dilated papillary dermal vessels

### Sézary Syndrome

- Clinical: Erythrodermic patient
  - Often without islands of sparing
  - Color lacks orange hue of PRP
- Histopathologic findings
  - Often nonspecific: Irregular acanthosis, superficial perivascular lymphocytic infiltrate
- Flow cytometry often necessary to make diagnosis

### Dermatomyositis

- Clinical
  - Rarely, dermatomyositis presents with erythroderma
  - Dermatomyositis often involves scalp/face and photodistributed areas
  - Unlike PRP, dorsal hand involvement accentuated over the joints (Gottron sign/papules)
- Histopathologic findings
  - Subtle interface vacuolar changes with occasional necrotic keratinocytes, sparse inflammation
- Serologies may be helpful (e.g., anti-Jo1 antibodies)

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## KEY FACTS

### TERMINOLOGY

- Acquired, asymptomatic, disfiguring dermatosis that primarily affects persons of Latin American or Asian ancestry and presents as asymptomatic, slowly progressive, gray-blue to brown hyperpigmented macules.

### CLINICAL ISSUES

- Usually symmetric ashy gray to hyperpigmented brown macules presenting on trunk, proximal extremities, and rarely face of persons with skin types III and IV
- Slow-progressing, asymptomatic, gray-blue to brown hyperpigmented macules
- Lesions are usually symmetric and can vary in shape and size: Usually oval, measuring 1-3 cm but can be larger

### MICROSCOPIC

- Active lesions can have lichenoid tissue reaction with basal vacuolar change reminiscent of lichen planus

- Inactive lesions can have normal-appearing to atrophic-looking epidermis with pigment incontinence in superficial dermis

### TOP DIFFERENTIAL DIAGNOSES

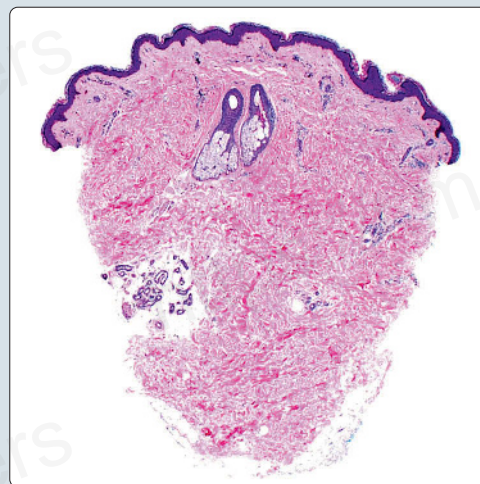
- Fixed drug eruption
  - Vacuolar interface dermatitis consisting of polymorphous infiltrate with eosinophils and lymphocytes
  - Chronic stage has papillary dermal fibrosis, pigment incontinence
- Postinflammatory hyperpigmentation
  - Increased melanin pigment in basal layer of epidermis
  - Rare pigment incontinence
  - Lymphocytes can be seen in dermis

Ashy Dermatoses

(Left) *Erythema dyschromicum perstans* presents as multiple gray-blue (ashy) to brown hyperpigmented macules involving the upper extremities of a person with skin type III. (Courtesy D. Loo, MD.) (Right) *Erythema dyschromicum perstans* can show a virtually normal-appearing biopsy at low power.

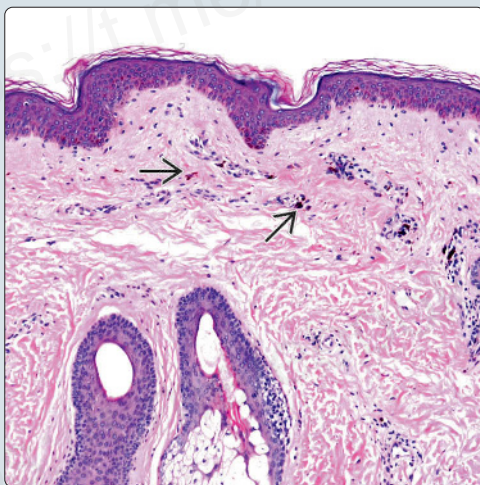


Seemingly Normal Biopsy on Low Power

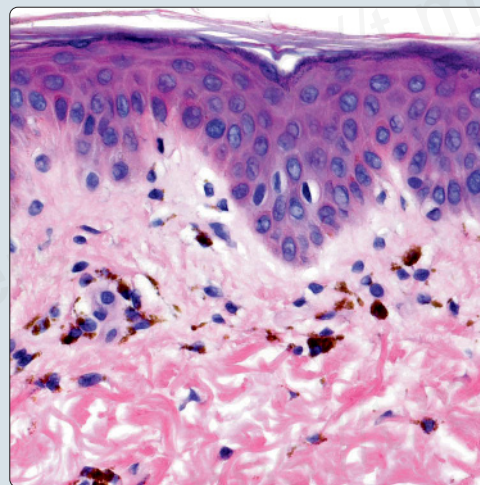


Pigment Incontinence Papillary Dermis

(Left) Histology of inactive *erythema dyschromicum perstans* shows pigment incontinence within the superficial dermis. (Right) High-power H&E of inactive *erythema dyschromicum perstans* shows pigment incontinence within the superficial dermis.



High-Power Pigment Incontinence





## TERMINOLOGY

### Synonyms

- Ashy dermatosis, ashy dermatitis, lichen planus pigmentosus, los cenicientos, dermatosis cenicienta

### Definitions

- Acquired, asymptomatic, disfiguring dermatosis that primarily affects persons of Latin American or Asian ancestry and presents as asymptomatic, slowly progressive, gray-blue to brown hyperpigmented macules

## ETIOLOGY/PATHOGENESIS

### Unknown

- Associations have been observed
  - Temporal associations with ingested agents: Ammonium nitrate, contrast medium
  - Temporal associations with infections: Whipworm, HIV, hepatitis C
  - Temporal associations (other conditions): Bronchial carcinoma, lichen planus, lichen planopilaris, endocrinopathies

## CLINICAL ISSUES

### Epidemiology

- Age
  - Can affect all ages (childhood through adulthood) but usually in 1st-3rd decades
- Sex
  - No gender predilection
- Ethnicity
  - Predominantly reported in Latin America or India, generally affecting skin types III and IV

### Site

- Trunk and proximal extremities usually affected, less frequently head and neck; usually spares palms and soles

### Presentation

- Slow-progressing, asymptomatic, gray-blue to brown hyperpigmented macules
- Active lesions can have 1- to 2-mm erythematous peripheral borders
  - Erythematous borders usually disappear after many months
- Inactive lesions have gray-blue (ashy) to brown hyperpigmentation
- Lesions are usually symmetric and can vary in shape and size: Usually oval, measuring 1-3 cm but can be larger

### Treatment

- Most treatments are unsuccessful, although following have been tried
  - Topical hydroquinone, steroids, retinoids, vitamin C, sun protectants, oral antibiotics, oral vitamin A, and dapsone

### Prognosis

- Many cases persist; active progression can last years; children are more likely to have resolution than adults

## MICROSCOPIC

### Histologic Features

- Active lesions: Mild, primarily lymphocytic lichenoid tissue reaction with basal vacuolar change and Civatte bodies
- Inactive lesions: Prominent melanin incontinence and variable epidermal changes (atrophy and effacement of rete ridges)

## ANCILLARY TESTS

### Immunofluorescence

- Active lesions: Direct immunofluorescence of colloid bodies with IgM, IgG, fibrinogen, and C4 has been reported

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Fixed drug eruption
  - Vacuolar interface dermatitis consisting of polymorphous infiltrate with eosinophils and lymphocytes
  - Acute stage has normal epidermis
  - Chronic stage has papillary dermal fibrosis, pigment incontinence
- Postinflammatory hyperpigmentation
  - Increased melanin pigment in basal layer of epidermis
  - Rare pigment incontinence
  - Lymphocytes can be seen in dermis

### Clinical

- Postinflammatory hyperpigmentation
  - Usually follows dermatitis of several weeks to months duration
- Multiple fixed drug eruption
  - Clinical history of tender red plaques that occur soon after drug ingestion
- Pityriasis rosea
  - Occurs generally in children and young adults as salmon-colored herald patch followed by secondary smaller scaly patches in Christmas tree distribution; resolves spontaneously
- Small plaque parapsoriasis
  - Presents as erythematous scaly patches favoring trunk, proximal extremities
- Macular urticaria pigmentosa
  - If it begins in childhood (< 10), it tends to resolve by adolescence; if it begins in adulthood, it will likely persist throughout life; pruritus is common
- Late pinta
  - Early lesions are papulosquamous, endemic to Central and South America, and caused by *Treponema carateum*
- Tinea versicolor
  - Can get hypopigmentation with KOH(+) scraping demonstrating hyphal forms

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3. Tisack AM et al: Erythema dyschromicum perstans in a Caucasian pediatric patient. *J Drugs Dermatol*. 12(7):819-20, 2013

## KEY FACTS

### TERMINOLOGY

- Linear dermatosis of childhood

### CLINICAL ISSUES

- Asymptomatic linear collection of pink to skin-colored papules erupting along lines of Blaschko
- Usually affects young children ages 9 months to 9 years
  - Females are affected more than males
- Occurs unilaterally
  - Extremities or trunk are typically involved
- Spontaneously resolves within months to years

### MICROSCOPIC

- Lichenoid reaction pattern
  - Composed of lymphocytes, histiocytes, and melanophages
  - Can involve hair follicles
  - Usually extends into eccrine glands
- Mild spongiosis and acanthosis

- Occasional hyperkeratosis and parakeratosis can be seen
- Dyskeratotic keratinocytes at any level is not uncommon
- Direct immunofluorescence is negative

### TOP DIFFERENTIAL DIAGNOSES

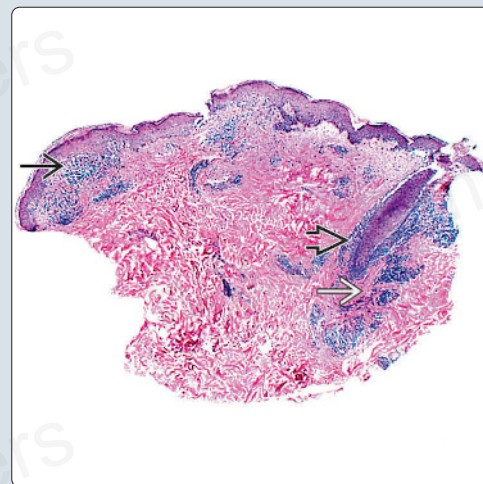
- Linear lichen planus
  - More intense inflammatory infiltrate than lichen striatus (LS)
  - Inflammatory infiltrate tends to be limited to superficial dermis (vs. LS, which extends deeper)
  - Dyskeratotic cells throughout epidermis are uncommon (vs. LS)
- Blaschkitis
  - Similar histologic features of LS but occurs in adults

Lichen Striatus Along Blaschko Lines

(Left) Lichen striatus (LS) is shown presenting as a single linear eruption of pink papules that follows along the lines of Blaschko on the lower extremity of a young female. (Courtesy P. Lio, MD.) (Right) LS demonstrates lichenoid reaction pattern composed of lymphocytes, histiocytes, and melanophages with overlying acanthosis and mild spongiosis. The infiltrate can involve hair follicles and the eccrine glands.

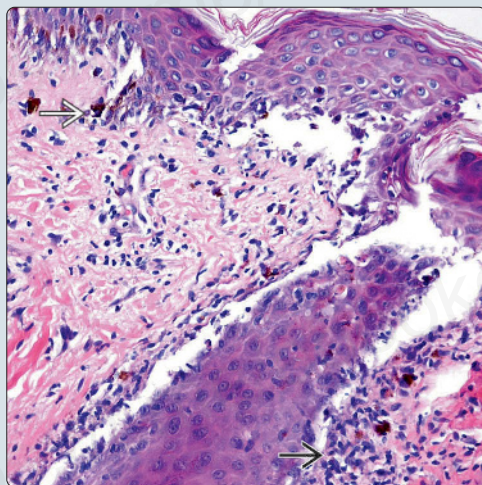


Lichenoid Reaction Pattern Includes Adnexa

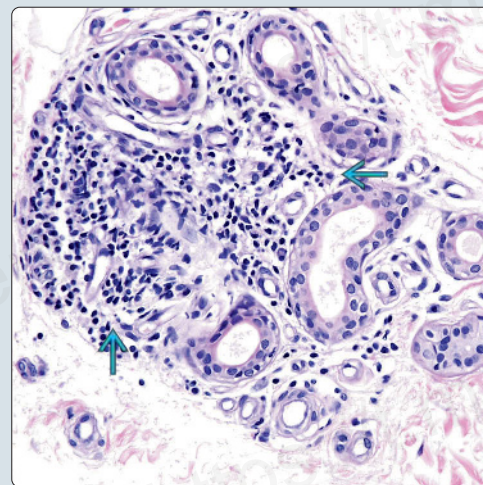


Melanophages Along Dermoepidermal Junction

(Left) Lymphohistiocytic infiltrate with scattered melanophages involves the dermoepidermal junction and follicular unit. (Right) In LS, it is common to have involvement of eccrine glands.



Lymphocytic Infiltrate Involving Eccrine Glands





## TERMINOLOGY

### Abbreviations

- Lichen striatus (LS)

### Synonyms

- Blaschko linear acquired inflammatory skin eruption
- Linear lichenoid dermatosis

### Definitions

- Uncommon, self-limited, asymptomatic, papular linear dermatosis that typically occurs unilaterally on extremities or trunk of young children along lines of Blaschko

## ETIOLOGY/PATHOGENESIS

### Etiology Remains Unknown

- Clustering in spring and summer months suggests environmental or infectious cause
- Occurrence along Blaschko lines suggests possible cell-mediated autoimmune reaction

## CLINICAL ISSUES

### Epidemiology

- Age
  - Occurs in young children often between 9 months and 9 years of age
- Sex
  - F > M

### Site

- Commonly presents on extremities or trunk and rarely head
- Nail changes are rare

### Presentation

- Typically presents suddenly as unilateral and asymptomatic pink to skin-colored, flat-topped papules erupting along lines of Blaschko
- Seasonal clustering in spring and summer months has been observed
- 1/3 of cases present with pruritus

### Treatment

- Symptomatic treatment with topical corticosteroids
- Tacrolimus should be considered for lesions involving face

### Prognosis

- Usually resolves spontaneously within 6 months, although rare cases can persist longer
- Hypopigmentation has been reported in 30-50% of cases
  - Hyperpigmentation can occur, albeit less frequently
- Relapses are uncommon

## MICROSCOPIC

### Histologic Features

- Lichenoid reaction pattern with inflammatory infiltrate, usually less dense than in lichen planus, composed of lymphocytes, histiocytes, and melanophages
- Acanthosis, spongiosis, and lymphocytic exocytosis
- Can have dyskeratotic keratinocytes at all levels of epidermis

- Mild hyperkeratosis and focal parakeratosis are not infrequent
- Inflammatory infiltrate can extend around hair follicles
- Extension of inflammatory infiltrate into surrounding eccrine glands is common
- Direct immunofluorescence is negative except for Civatte bodies

## ANCILLARY TESTS

### Immunofluorescence

- IgM, IgA, or C3 (+) Civatte bodies on direct immunofluorescence

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Linear lichen planus
  - More intense inflammatory infiltrate than LS
    - Inflammatory infiltrate tends to be limited to superficial dermis (vs. LS, which extends deeper)
  - Dyskeratotic cells throughout epidermis are uncommon (vs. LS)
  - Spongiosis is not seen (vs. LS)
  - Parakeratosis is not seen (vs. LS)
- Blaschkitis
  - Similar histologic features of LS but occurs in adults

### Clinical

- Linear lichen planus
  - Usually more pruritic than LS
  - Patients tend to have more hyperpigmentation sequela than hypopigmentation (opposite trend is seen in LS)
- Blaschkitis
  - Similar appearance of LS but is seen in adults
- Incontinentia pigmenti
  - X-linked genodermatosis that affects females in 1st few weeks of life with cutaneous, neurologic, ophthalmologic, and dental manifestations
    - Evolves through various stages: Vesicular, verrucous, pigmented (hyperpigmented and hypopigmented)
    - Involves lines of Blaschko

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## KEY FACTS

### TERMINOLOGY

- Lymphohistiocytic inflammatory infiltrate

### ETIOLOGY/PATHOGENESIS

- Unknown etiology

### CLINICAL ISSUES

- Multiple discrete, red to skin-colored, flat-topped or dome-shaped papules involving upper flexural areas, anterior trunk, and genitalia

### MICROSCOPIC

- Classic ball and claw morphology of lymphohistiocytic inflammatory infiltrate with acanthotic rete ridges and atrophic epidermis

### TOP DIFFERENTIAL DIAGNOSES

- Histopathologic
  - Lichen planus
  - Early lichen scrofulosorum

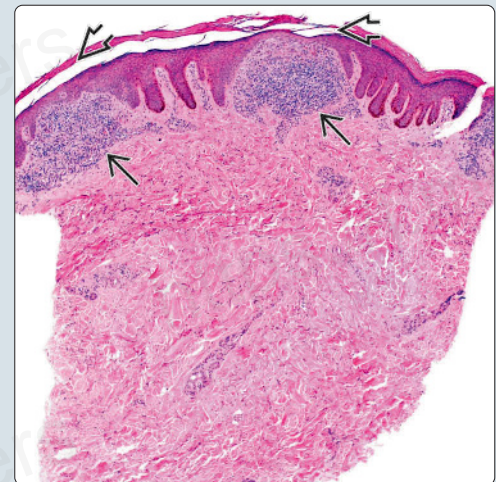
- Granulomas do not cause widening of dermal papillae (lichen nitidus does)
- Langerhans cell histiocytosis
  - Can present with dermal and intraepidermal collections of Langerhans cells
- Clinical
  - Keratosis pilaris
    - Follicular distribution with conspicuous plugging
  - Papular eczema
    - Atopic history, F > > M, before age of 5, mostly in persons of African or Asian descent
  - Verrucae plana
    - Not uncommon in young children and can have linear configuration following autoinoculation

### Monomorphic, Dome-Shaped Papules

(Left) Multiple discrete, pink, and dome-shaped, monomorphic papules involving the dorsal hands of a young person with skin-type IV are shown. (Courtesy D. Loo, MD.) (Right) Discrete inflammatory infiltrates forming ball-like aggregates within the superficial dermis are shown. The overlying epidermis is atrophic with mild hyperkeratosis and parakeratosis.

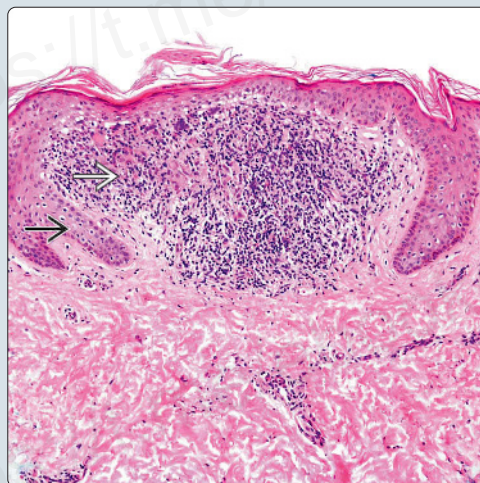


### Ball in Claw

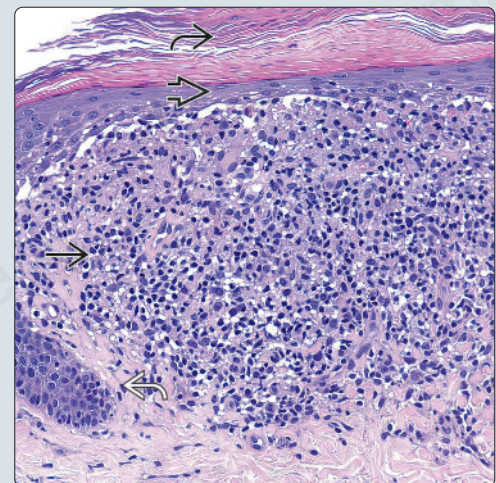


### Acanthotic Rete Ridges

(Left) This image shows acanthotic rete ridges forming a claw-like grasp around the ball-like aggregate of the superficial dermal inflammatory infiltrate. (Right) Claw-like acanthotic rete ridge surrounding the ball-like lymphohistiocytic infiltrate is shown. Note the overlying atrophic epidermis with hyperkeratotic and parakeratotic scale.



### Lymphohistiocytic Infiltrate





**TERMINOLOGY****Abbreviations**

- Lichen nitidus (LN)

**Definitions**

- Uncommon asymptomatic inflammatory dermatosis consisting of multiple, tiny, discrete, skin-colored papules affecting mainly children and young adults

**ETIOLOGY/PATHOGENESIS****Unknown**

- Associations with amenorrhea, Crohn disease, HIV, atopic dermatitis, and hepatitis B vaccination have been observed

**CLINICAL ISSUES****Epidemiology**

- Incidence
  - Rare
    - 1 older study involving African Americans over 25-year period suggests incidence of 0.034%
- Age
  - Predominantly children and young adults are affected
- Sex
  - Both genders equally affected
- Ethnicity
  - No ethnic predilection

**Site**

- Flexor aspect of upper extremities, chest, abdomen, or genitals

**Presentation**

- Skin
  - Eruption of multiple discrete, red to pink, or flesh-colored flat-topped &/or dome-shaped papules
  - Generally asymptomatic; occasionally pruritic; koebnerization phenomenon expected and accounts for linear arrays of papules; postinflammatory hyperpigmentation can occur
  - Photodistribution subtype (a.k.a. actinic LN)
    - Typically occurs during summer months, frequently overlapping with actinic lichen planus and occurring most frequently in subtropical regions (e.g., Middle East, India)
  - Generalized subtype
    - Koebnerization phenomenon is more prevalent in this subtype, as well as reported female predominance
- Nails: Occurs in 10% of cases; presents as pitting, rippling, thickening of longitudinal ridges, or terminal splitting
- Mucous membranes: Presents as grayish yellow papules

**Treatment**

- Primarily symptomatic in nature
  - Topical steroids or oral antihistamines for pruritus; anecdotal use of topical tacrolimus for children; antituberculous agents; low-dose cyclosporine; narrow band ultraviolet B; avoidance of sun exposure for those with actinic LN

**Prognosis**

- Majority of patients experience spontaneous resolution of lesions within 1 or several years

**MICROSCOPIC****Histologic Features**

- Sharply circumscribed, dense, subepidermal infiltrate limited to 1-2 adjacent dermal papillae
  - Inflammatory infiltrate is composed of lymphocytes, histiocytes, melanophages, and occasional giant cells
- Acanthotic rete ridges forming claw-like epidermal grasp around ball-like inflammatory infiltrate
- Epidermis overlying inflammatory infiltrate is often atrophic
  - Parakeratotic scale is often present and epidermis can show basal cell hydropic degeneration

**ANCILLARY TESTS****Immunofluorescence**

- Direct immunofluorescence is usually negative

**DIFFERENTIAL DIAGNOSIS****Histopathologic**

- Lichen planus
  - Lacks parakeratosis and ball and claw inflammatory infiltrate morphology
  - Prominent hypergranulosis and Civatte bodies, which stain with IgM, IgA, or C3 on direct immunofluorescence
- Lichen scrofulosorum
  - Granulomas do not cause widening of dermal papillae (LN does)
- Langerhans cell histiocytosis
  - Can present with dermal and intraepidermal collections of Langerhans cells
    - Cells show round, pale, and granular eosinophilic cytoplasm with reniform-shaped nucleus
    - Cells stain positive for S100 and CD1a

**Clinical**

- Lichen planus: Commonly pruritic, affects oral mucosa (Wickham striae) and nails more than LN
- Keratosis pilaris: Follicular distribution with conspicuous plugging
- Verrucae plana: Not uncommon in young children and can have linear configuration following autoinoculation
- Papular eczema: Atopic history, F > > M, before age of 5, mostly in persons of African or Asian descent
- Lichen amyloidosis: Severely pruritic papules or plaques occurring on anterior shins, extensor aspects of forearms; typically found in persons of Asian descent

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## KEY FACTS

### TERMINOLOGY

- Phototoxic reaction to furocoumarins from plants

### ETIOLOGY/PATHOGENESIS

- Ultraviolet A radiation, in conjunction with plant-derived psoralens, induces this phototoxic reaction

### MICROSCOPIC

- Histology of active lesions is same as that of other phototoxic reactions including those due to drugs: Vacuolar change, keratinocyte necrosis, and "sunburn cells"

### TOP DIFFERENTIAL DIAGNOSES

- Fixed drug eruption (FDE)
  - Basal layer dyskeratosis and lichenoid inflammation are present in FDE
  - Eosinophils are common in FDE but not phytophotodermatitis (PPDT)
- Allergic contact dermatitis
  - More of clinical differential diagnosis

- PPDT features necrosis and vacuolar change and lacks Langerhans cell microabscesses and eosinophils
- Postinflammatory hyperpigmentation (PIH)
  - Late lesions are indistinguishable
  - Early or active lesions of PPDT will have keratinocyte necrosis or vacuolar change (not seen in PIH)
- Phototoxic drug reaction
  - May not be possible to distinguish sunburns and phototoxic drug reactions from PPDT
- Photoallergy
  - Primary spongiotic process and lacks necrosis

### DIAGNOSTIC CHECKLIST

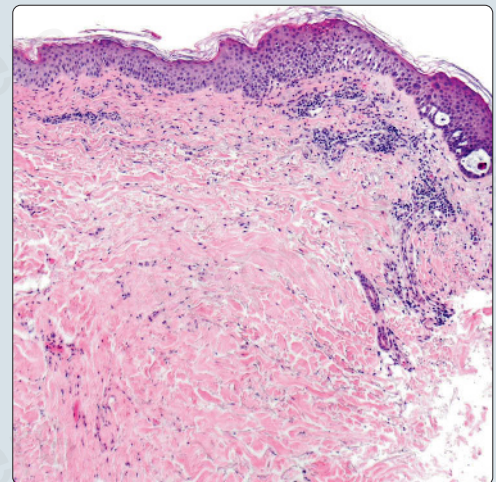
- In active or acute lesions, look for necrosis limited to upper epidermis and "sunburn cells"

### Streaky Geometric Hyperpigmentation

(Left) *Phytophotodermatitis shows streaky, geometric hyperpigmentation on the thigh. (Courtesy S. Hsu, MD.)*  
(Right) *Low-power view of the acute phase of phytophotodermatitis demonstrates spongiosis with necrotic keratinocytes.*

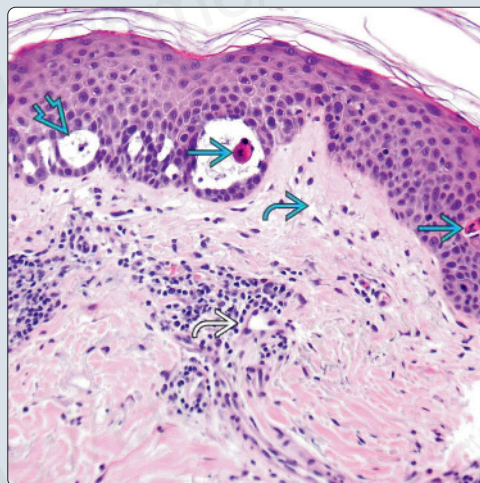


### Spongiosis and Necrotic Keratinocytes

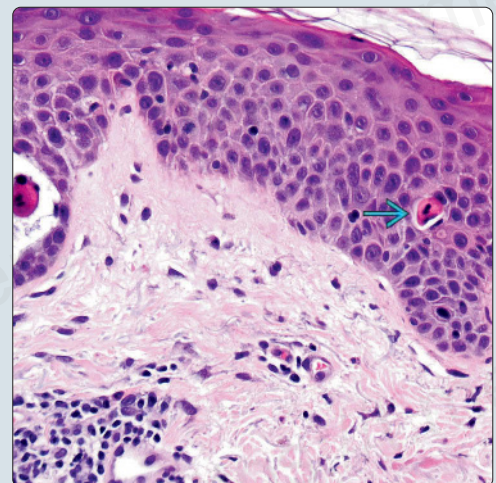


### Spongiosis, Dyskeratotic Keratinocytes, and Edema

(Left) *Histology of the acute phase of phytophotodermatitis is that of a phototoxic reaction: Spongiosis with dyskeratotic cells above the basal layer ("sunburn cells"), papillary dermal edema, and dilated blood vessels.* (Right) *"Sunburn cells" or necrotic keratinocytes in the upper layers of the epidermis are a clue to phototoxic reactions.*



### "Sunburn Cells"





## TERMINOLOGY

### Abbreviations

- Phytophotodermatitis (PPDT)

### Synonyms

- Berloque dermatitis, lime disease, margarita dermatitis, strimmer rash

### Definitions

- PPDT is nonimmunologic phototoxic reaction to furocoumarins, naturally occurring plant-derived psoralens

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- Given that psoralens have action spectrum in range of 315-375, ultraviolet A radiation induces this phototoxic reaction
  - Following absorption of furocoumarin, photoproduct is formed that results in keratinocyte injury
  - In experimental animal models, ultrastructural changes, including vacuolar change, membrane degeneration, and disruption of desmosomes, are seen within 2 hours
  - Keratinocyte necrosis and blister formation occur within 24-48 hours
- Plants belonging to family Umbelliferae are most common causative agents and include celery, parsley, and hogweed
  - Citrus family (Rutaceae) are also common causes and include lime as well as oil of bergamot, which was historically used in perfumes, resulting in "berloque dermatitis"
  - Moraceae family (includes fig) is also causative

## CLINICAL ISSUES

### Presentation

- Patients present with linear or geometric and painful, dusky plaques in exposed areas, which then hyperpigment
- In intense reactions, vesiculation due to keratinocyte necrosis may result in dramatic bullous lesions
- Unlike allergic contact dermatitis, pruritus is uncommon

### Treatment

- Drugs
  - Wet compresses and topical steroids can be used for symptomatic, edematous eruptions
  - Topical hydroquinones may be used for persistent hyperpigmentation, although this may not be effective or necessary

### Prognosis

- PPDT is benign and self-limited, although subsequent postinflammatory hyperpigmentation may be long-lasting

## MICROSCOPIC

### Histologic Features

- PPDT is generally clinical diagnosis given that characteristic hyperpigmentation is usually only clinical finding by time most patients present to dermatologist
- Experimentally induced PPDT in animal models with postexposure serial microscopy demonstrate spongiosis with isolated or confluent keratinocyte necrosis and vacuolar change at 24 hours

- At 48 hours, vacuolization with sub- or intraepidermal blisters form
- At 72 hours, vacuolization and spongiosis are less marked, but atypical cells with irregular nuclei ("sunburn cells") appear

## DIFFERENTIAL DIAGNOSIS

### Fixed Drug Eruption

- Active lesions can be discriminated: Although PPDT demonstrates vacuolar change, necrotic keratinocytes are placed in spinous and granular layers of epidermis
  - In contrast, basal layer dyskeratosis and lichenoid inflammation are present in fixed drug eruption (FDE)
- Eosinophils are common in FDE but not PPDT
- Late lesions (postinflammatory hyperpigmentation) cannot be discriminated

### Allergic Contact Dermatitis

- Should only cause confusion clinically, although
- Spongiosis and vesiculation are common to both
- PPDT features necrosis and vacuolar change and lacks Langerhans cell microabscesses and eosinophils

### Postinflammatory Hyperpigmentation

- Early or active lesions of PPDT will have keratinocyte necrosis or vacuolar change
- Late lesions are indistinguishable

### Other Phototoxic Reactions, Including Phototoxic Drug Reaction

- It may not be possible to distinguish sunburns and phototoxic drug reactions from PPDT
- Variable edema, vasodilation, superficial perivascular lymphocytic infiltrates may be seen
- Vacuolar change, keratinocyte necrosis in upper layers of epidermis and "sunburn cells" are common features
- Exocytosis of neutrophils may also be seen

### Photoallergy

- Clinical distribution is similar but photoallergy is primary spongiotic process and lacks necrosis
- Features may be indistinguishable from those of allergic contact dermatitis

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Vacuolar change and keratinocyte necrosis
- Pigment incontinence and melanophages

### Pathologic Interpretation Pearls

- Look for necrosis limited to upper portion of epidermis and "sunburn cells" with irregular or large nuclei

## SELECTED REFERENCES

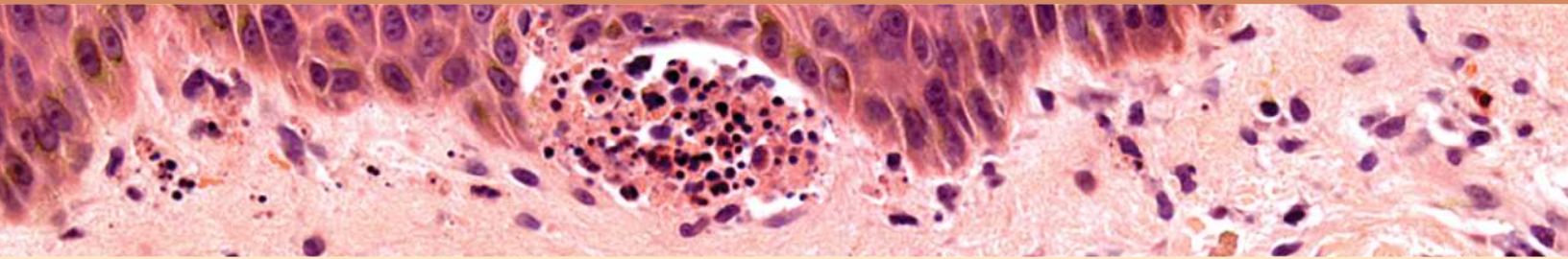
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## SECTION 3

# Vesiculobullous Dermatoses



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# Bullous Pemphigoid

## KEY FACTS

### ETIOLOGY/PATHOGENESIS

- Autoantibodies to BPAG1 and BPAG2 on hemidesmosomes at dermal-epidermal junction (DEJ)
- Drug-induced pemphigoid: Induced by diuretics (furosemide), captopril, D-penicillamine, antibiotics (amoxicillin), gold, potassium iodide, anti-TNF $\alpha$

### CLINICAL ISSUES

- Generally symmetric pruritic vesicles and tense bullae 1-4 cm in diameter most commonly on lower abdomen, forearms, and thighs
- Early lesions may appear urticarial
- Only rare mucosal involvement (~ 10-30% of cases)
- Chronic disease with remissions and exacerbations

### MACROSCOPIC

- Tense bullae with severe pruritus

### MICROSCOPIC

- Subepidermal cleft or bullae with abundant eosinophils

- Superficial and interstitial perivascular lymphocytic, eosinophilic, and neutrophilic infiltrate
- Cell poor bullous pemphigoid (BP): Subepidermal bulla with paucity of inflammation
- Urticarial BP: Dermal edema with eosinophils


### ANCILLARY TESTS

- Direct immunofluorescence of perilesional skin shows linear deposition IgG &/or C3 at DEJ
- Salt-split skin distinguishes between BP and EBA
- ELISA demonstrates serum level of IgG, which correlates to disease severity

### TOP DIFFERENTIAL DIAGNOSES

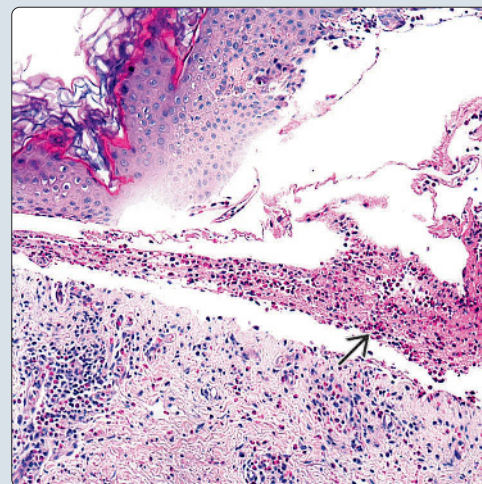
- Pemphigus vulgaris
- Epidermolysis bullosa acquisita
- Linear IgA bullous dermatosis
- Pemphigoid gestationis
- Bullous lupus erythematosus

**Tense Fluid-Filled Vesicles**


**(Left)** Bullous pemphigoid (BP) clinically demonstrates multiple tense fluid-filled vesicles and bullae covering the lower legs and abdomen. (Courtesy V. Newcomer Collection at UCLA and Logical Images, Inc.) **(Right)** This biopsy of BP demonstrates a typical subepidermal blister with numerous eosinophils within . Note that eosinophils as well as a monomorphous infiltrate are also present in the dermis.

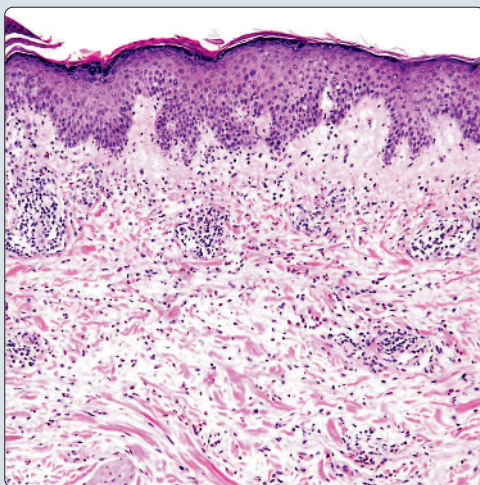


**Subepidermal Blister With Eosinophils**

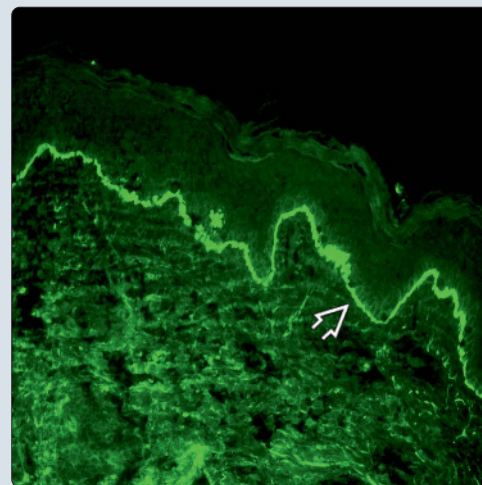


**Eosinophils in Superficial Dermis**

**(Left)** Early urticarial BP demonstrates superficial perivascular and interstitial mixed inflammatory infiltrates. Numerous eosinophils (more obvious at a higher power) are present. **(Right)** Direct immunofluorescence of BP characteristically demonstrates linear IgG  &/or C3 at the dermal-epidermal junction.



**Linear IgG**



## TERMINOLOGY

### Abbreviations

- Bullous pemphigoid (BP)

### Synonyms

- Pemphigoid

### Definitions

- Autoimmune blistering disease of skin

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- Drug-induced pemphigoid: Induced by diuretics (furosemide), captopril, D-penicillamine, antibiotics (amoxicillin), gold, potassium iodide, anti-TNF- $\alpha$

### Autoimmunity

- IgG antibodies against BP antigen 1 (BPAG1; BP230) and BP antigen 2 (BPAG2; BP180; type XVII collagen) of hemidesmosome junctional adhesion complexes at dermal-epidermal junction (DEJ)

### Malignancy

- Rarely associated with underlying malignancy

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - 5-13 cases per 1 million people per year
  - Usually affects adults or elderly ( $\geq 60$  years)
  - Higher incidence in men than women

### Presentation

- Generally symmetric pruritic vesicles and tense bullae 1-4 cm in diameter most commonly on lower abdomen, forearms, and thighs
- Only rare mucosal involvement (~ 10-30% of cases)

### Treatment

- Drugs
  - Systemic corticosteroids
  - Steroid-sparing agents
    - Azathioprine, methotrexate, cyclophosphamide, chlorambucil, cyclosporine, mycophenolate mofetil, nicotinamide, rituximab
  - Topical therapy: Corticosteroids, tacrolimus/pimecrolimus

## MICROSCOPIC

### Histologic Features

- Subepidermal cleft or bulla with numerous eosinophils
- Superficial and interstitial perivascular lymphocytic, eosinophilic, and neutrophilic infiltrate
- Cell poor BP: Subepidermal bulla with paucity of inflammation
- Urticarial BP: Dermal edema with eosinophils

## ANCILLARY TESTS

### Immunofluorescence

- Direct immunofluorescence (DIF) of perilesional skin shows linear deposition IgG and/or C3 at DEJ
- Indirect immunofluorescence (IIF): Detects circulating IgG and occasionally IgA in patient's sera to salt-split normal human skin
  - Salt-split skin-linear deposition of antibodies on epidermal fragment (roof of blister)

### Serologic Testing

- Immunoblotting and immunoprecipitation demonstrate IgG in patient's sera binding to 180-kDa and 230-kDa proteins, which correspond to BPAG2 and BPAG1, respectively
- ELISA demonstrates serum level of IgG, which correlates to disease severity

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- **Epidermolysis bullosa acquisita**
  - IIF salt-split with linear deposition of antibodies on floor of blister
- **Linear IgA bullous dermatosis**
  - Typically with abundance of neutrophils
  - DIF shows linear deposition of IgA at DEJ
- **Pemphigus vulgaris**
  - Suprabasilar acantholysis
- **Cicatricial pemphigoid**
  - Subepidermal bullae with associated dermal fibrosis

### Clinical

- **Pemphigoid gestationis**
  - Variant of BP that occurs in pregnancy (typically 3rd trimester) or immediately postpartum
  - Lesions begin periumbilically and subsequently generalize
- **Epidermolysis bullosa acquisita**
  - Milia, tense vesicles and bullae
  - Typically more paucicellular than pemphigoid and with fewer eosinophils
  - More recalcitrant to therapy than BP
- **Pemphigus vulgaris**
  - Superficial erosions and flaccid bullae
- **Linear IgA dermatosis**
  - Lesions often clustered in rosette or crown of jewels pattern

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# Pemphigus and Variants

## KEY FACTS

### ETIOLOGY/PATHOGENESIS

- Autoantibodies to keratinocyte adhesion molecules

### MACROSCOPIC

- Nikolsky sign: Induction of new blister with slight friction
- Asboe-Hansen sign: Lateral extension of intact blister with gentle pressure
- Flaccid bullae with crusted plaques and erosions

### MICROSCOPIC

- Intraepidermal acantholysis
- Tombstoning of basal keratinocytes in pemphigus vulgaris
- Often eosinophils present

### ANCILLARY TESTS

- Direct immunofluorescence of perilesional skin displays pattern of IgG &/or C3 against keratinocyte adhesion molecules, chicken-wire pattern
- Indirect immunofluorescence and ELISA: Correlate with disease activity

### TOP DIFFERENTIAL DIAGNOSES

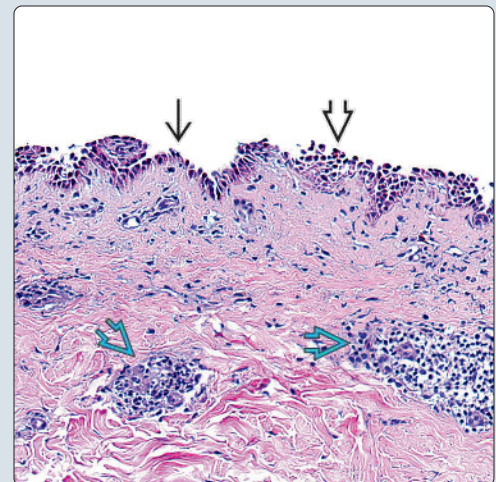
- Histologic
  - Hailey-Hailey disease
  - Grover disease
  - Bullous impetigo
  - Darier disease
  - Acantholytic acanthoma
  - Warty dyskeratoma
- Clinical
  - Bullous pemphigoid
  - Linear IgA bullous dermatosis
  - Bullous lupus erythematosus
  - Cicatricial pemphigoid
  - Epidermolysis bullosa acquisita
  - Bullous drug eruption

**Crusted Erosions of Pemphigus Vulgaris**

(Left) In this image from the back, pemphigus vulgaris clinically demonstrates crusted plaques and superficial erosions with occasional retained flaccid bullae. (Right) This biopsy of pemphigus vulgaris shows suprabasilar acantholysis and characteristic tombstoning of the papillary dermis with retained basilar keratinocytes. Note the associated dermal perivascular infiltrate.

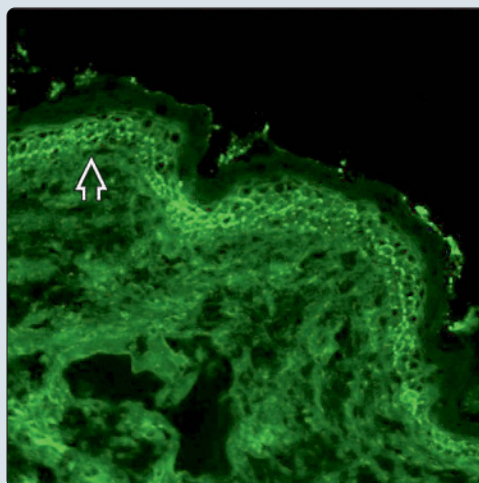


**Acantholytic Blister With Tombstoning**

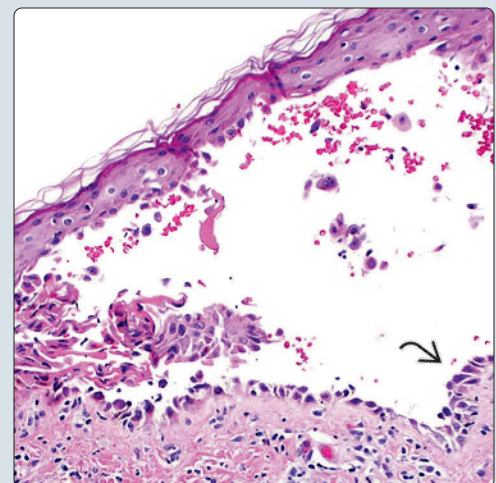


**Intercellular C3 on Immunofluorescence**

(Left) Direct immunofluorescence reveals an intercellular network of immunoreactants (IgG and C3) in pemphigus vulgaris. Signal intensity is strongest near the base. (Right) In pemphigus vulgaris, an intraepidermal blister is created because of suprabasilar acantholysis.



**Suprabasilar Acantholysis**



## TERMINOLOGY

### Definitions

- Autoimmune blistering disease of skin and mucous membranes
- **Pemphigus vulgaris (PV)**
  - Most common form of pemphigus with autoantibodies directed against desmoglein 3
  - Presents with cutaneous and mucosal erosions and flaccid bullae
- **Pemphigus vegetans**
  - Localized form of pemphigus vulgaris with hyperkeratotic plaques
  - Hallopeau type
    - More benign type of pemphigus vegetans requiring lower doses of corticosteroids and longer remissions
  - Neumann type
    - More severe type of pemphigus vegetans with similar clinical course and prognosis to PV
- **Pemphigus foliaceus (PF)**
  - Superficial form of pemphigus with autoantibodies directed against desmoglein 1
  - Crusted lesions typically involving the skin without mucosal involvement
- **Paraneoplastic pemphigus (PNP)**
  - Variant associated with underlying malignancy including non-Hodgkin lymphoma, leukemia, and Castleman disease
- **IgA pemphigus**
  - Intraepidermal neutrophilic (IEN) type and subcorneal pustular dermatosis (SPD) type
  - Presents with pruritic flaccid vesicles or pustules, often annular or circinate with central crust
- **Pemphigus erythematosus (PE)**
  - Overlap of lupus erythematosus and pemphigus presenting with crusted plaques often in malar distribution and with antibodies directed against intercellular and basement membrane antigens
- **Drug-induced pemphigus**
  - Variant presenting after exposure to drugs such as penicillamine and captopril

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- *Simulium* spp. (black fly): Possible vector for fogo selvagem (endemic pemphigus foliaceus) variant in Brazil

### Autoimmune

- Autoantibodies to keratinocyte adhesion antigens resulting in acantholysis (loss of cell-cell adhesion) and blister formation
  - Pemphigus vulgaris: IgG autoantibodies to desmoglein 3 (130 kDa)
  - Pemphigus foliaceus: IgG autoantibodies to desmoglein 1 (160 kDa)
  - Paraneoplastic pemphigus: IgG autoantibodies to plakins (BPAG1, envoplakin, periplakin, desmoplakin, plectin) and desmogleins 1 and 3
  - IgA pemphigus: IgA autoantibodies to desmocollin 1

### Malignancy

- PNP is associated with underlying malignancies
  - Age-appropriate cancer screening is indicated

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - 0.76-5 cases per 1 million per year worldwide
- Age
  - Adults, 40-60 years
  - Fogo selvagem variant affects mainly children and young adults
- Sex
  - Prevalence is equal in men and women
- Ethnicity
  - More common in those with Jewish ancestry
    - 16-32 cases per 1 million per year

### Presentation

- **PV:** Painful cutaneous and mucosal flaccid blisters and erosions, intact blisters are rare
  - Pemphigus vegetans: Flaccid blisters evolve into verrucous, fungating, pustular vegetations, especially intertriginous areas, scalp, and face
- **PF:** Crusted cutaneous erosions often in seborrheic distribution of head and neck, no intact blisters, mucosal involvement rare
  - May clinically mimic papulosquamous eruption
- **PNP:** Painful, recalcitrant stomatitis and conjunctival erosions, lichenoid-like and erythema multiforme-like cutaneous lesions that are typically acral
- **IgA pemphigus:** Pruritic flaccid vesicles or pustules, often annular or circinate with central crust
- **PE:** Crusted erosions in malar regions of face
- **Pemphigus herpetiformis:** Clinically resembles dermatitis herpetiformis with small grouped papulovesicles, intensely pruritic

### Treatment

- Options, risks, complications
  - Complications associated with long-term steroid use: Infection, osteoporosis, diabetes, cataracts
- Drugs
  - Systemic corticosteroids
  - Steroid-sparing agents
    - Mycophenolate mofetil, azathioprine, rituximab, cyclosporine, methotrexate, cyclophosphamide
  - Topical therapy
    - Corticosteroids, tacrolimus/pimecrolimus, antibiotics
  - Others
    - Rituximab, intravenous immunoglobulin (IVIg), extracorporeal photophoresis, plasmapheresis

### Prognosis

- Historically high mortality secondary to infection and sepsis
- Prognosis is now good with early initiation of steroid and steroid-sparing therapy

# Pemphigus and Variants

## MACROSCOPIC

### General Features

- Nikolsky sign
  - Induction of new blister with slight friction
- Asboe-Hansen sign
  - Lateral extension of intact blister with gentle pressure
- Flaccid bullae with crusted plaques and erosions

## MICROSCOPIC

### Histologic Features

- **PV**
  - Intraepidermal vesicle with suprabasilar acantholysis
    - Blister cavity contains round acantholytic keratinocytes
    - Tombstone appearance: Basal keratinocytes retain attachment to basement membrane by way of hemidesmosome but lose attachment to neighboring keratinocytes
  - Eosinophilic spongiosis: Eosinophils within epidermis
  - Acantholysis may extend down hair follicles
  - Dermal perivascular mononuclear infiltrate with eosinophils
  - Apoptotic keratinocytes are not regularly seen
- **Pemphigus vegetans** (Neumann and Hallopeau types)
  - Suprabasilar acantholysis with overlying papillomatosis and acanthosis
  - Intraepidermal microabscesses of eosinophils
- **PF, fogo selvagem, PE**
  - Subcorneal acantholysis usually involving granular layer, eosinophilic spongiosis
  - Neutrophilic exocytosis and dermal infiltrate including lymphocytes, eosinophils, neutrophils
- **PNP**
  - Features of pemphigus vulgaris, erythema multiforme, and lichen planus
  - Suprabasilar acantholysis, necrotic keratinocytes
  - Basal cell vacuolar change with lichenoid lymphocytic infiltrate, eosinophils rare
- **IgA pemphigus**
  - Intraepidermal vesicle or pustule containing numerous neutrophils
    - IEN type: Suprabasilar pustules
    - SPD type: Subcorneal pustules
  - Acantholysis is rare
- **Drug-induced pemphigus**
  - Often subcorneal acantholysis
  - Eosinophilic spongiosis, dermal eosinophils
- **Pemphigus herpetiformis**
  - Spongiosis with intraepidermal eosinophils and neutrophils, limited acantholysis

## ANCILLARY TESTS

### Immunofluorescence

- Direct immunofluorescence of perilesional skin is most sensitive tool to diagnosis pemphigus variants
  - PV: Intercellular IgG and C3 in lower epidermis in chicken-wire pattern

- PF: Intercellular IgG and C3 in upper epidermis in chicken-wire pattern
- PNP: Intercellular IgG and C3 in chicken-wire pattern as well as linear IgG at basement membrane
- IgA pemphigus: Intercellular IgA in epidermis in chicken-wire pattern
- PE: Both intercellular IgG in chicken-wire pattern and linear IgG at basement membrane
- Drug-induced pemphigus: Intercellular IgG in chicken-wire pattern
- Pemphigus herpetiformis: Intercellular IgG and C3 in upper or lower epidermis
- Indirect immunofluorescence detects circulating antibodies in patients' serum
  - PV: Autoantibodies directed against desmoglein 3 detected on monkey esophagus substrate
  - IgA pemphigus: Autoantibodies directed against keratinocyte cell surface substrate

### Serologic Testing

- Enzyme-linked immunosorbent assay (ELISA)
  - Detects circulating IgG to desmoglein 1 and desmoglein 3
  - ELISA titers correlates with disease activity

### Immunoprecipitation and Immunoblotting

- Detects antigens as protein band of specific molecular weight

## DIFFERENTIAL DIAGNOSIS

### Histopathologic Differential Diagnosis

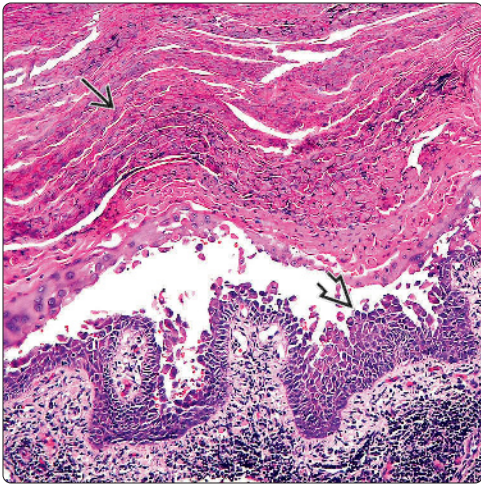
- Transient acantholytic dermatosis (Grover disease)
  - Smaller foci of acantholysis than pemphigus
  - Typically has "seborrheic" distribution clinically
  - Dyskeratosis and spongiosis common in Grover disease
- Bullous impetigo
  - Often has associated colonies of gram-positive cocci within blister cavities
  - Associated golden yellow crust clinically
- Benign familial pemphigus (Hailey-Hailey disease)
  - Acantholysis with dilapidated brick wall pattern extending through most layers of epidermis with relative sparing of basal layer
  - Lacks follicular acantholysis
  - Erosions often in intertriginous areas (e.g., axilla, inframammary, inguinal)
- Darier disease
  - More dyskeratosis than acantholysis
  - More associated acanthosis and parakeratosis
- Acantholytic acanthoma
  - Isolated lesion with acantholysis
- Warty dyskeratoma
  - Endophytic lesion with verrucous architecture and acantholytic dyskeratosis

## SELECTED REFERENCES

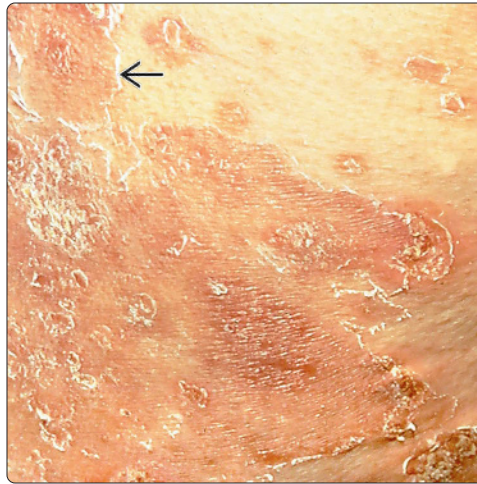
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**Pemphigus Vegetans**

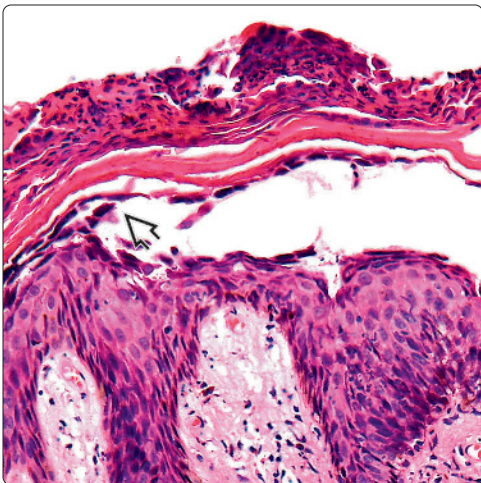


**Crusted Plaques of Pemphigus Foliaceus**

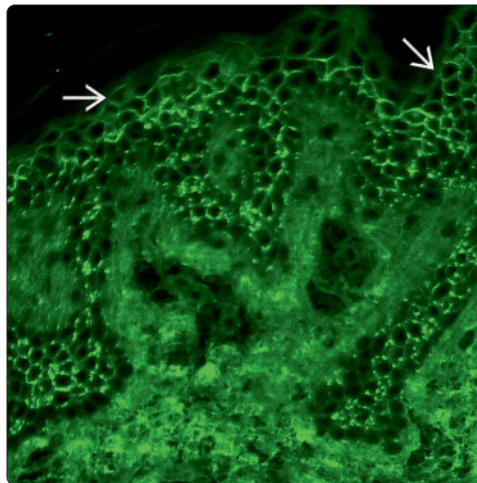


(Left) Biopsy of pemphigus vegetans demonstrates intraepidermal acantholysis [arrow] and marked acanthosis [green arrow]. Occasional eosinophilic pustules (not shown) can be seen. (Courtesy P. Sarantopoulos, MD.) (Right) Clinical photograph shows pemphigus foliaceus on the chest with annular superficial desquamation [arrow] instead of intact blisters. Pemphigus foliaceus mimics a papulosquamous dermatitis, most notably seborrhea, but the histopathology is dramatically different.

**Acantholysis in Granular Layer of Pemphigus Foliaceus**

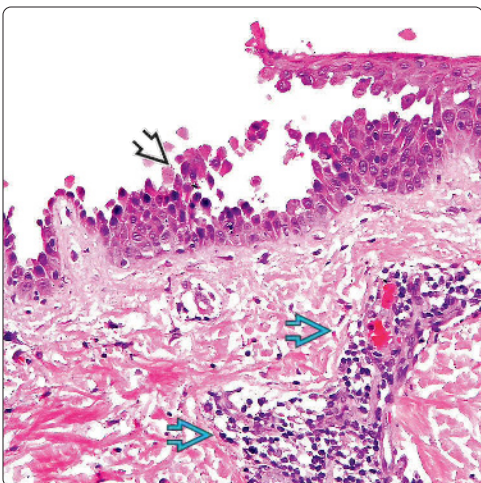


**Intercellular IgG in Pemphigus Foliaceus on Direct Immunofluorescence**

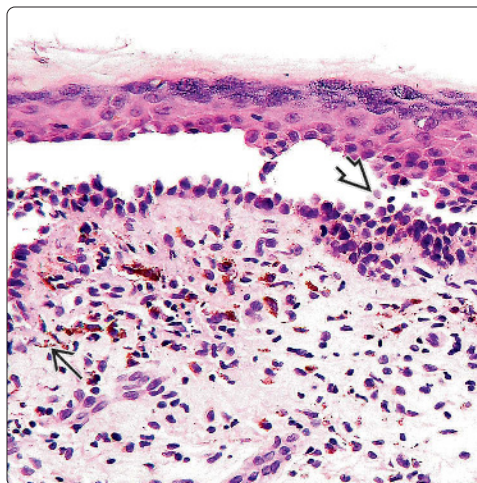


(Left) This biopsy of pemphigus foliaceus demonstrates subcorneal acantholysis [arrow]. (Courtesy P. Sarantopoulos, MD.) (Right) Direct immunofluorescence of pemphigus foliaceus demonstrates intercellular IgG in the upper epidermis in a chicken wire pattern [arrow]. (Courtesy P. Sarantopoulos, MD.)

**Intraepidermal Acantholysis in Pemphigus Erythematosus**



**Paraneoplastic Pemphigus: Suprabasilar Acantholysis and Necrotic Keratinocytes**



(Left) This biopsy of pemphigus erythematosus demonstrates intraepidermal acantholysis [arrow] and an associated dermal perivascular inflammatory infiltrate [green arrow]. (Courtesy P. Sarantopoulos, MD.) (Right) This biopsy of paraneoplastic pemphigus demonstrates suprabasilar acantholysis [arrow] with occasional necrotic keratinocytes and interface dermatitis [green arrow]. (Courtesy P. Sarantopoulos, MD.)



## KEY FACTS

### TERMINOLOGY

- Subepidermal blistering disorder characterized by intense pruritus
- Highly associated with gluten-sensitive enteropathy

### CLINICAL ISSUES

- Characteristically symmetrically involves elbows, knees, nape of neck, sacrum, scalp
- Vesicles rare, excoriations/erosions predominate

### MICROSCOPIC

- Early lesion
  - Papillary dermal microabscesses of predominantly neutrophils
- Later lesion
  - May see subepidermal split with numerous neutrophils in base
  - Dermal papillae adjacent to split often contain microabscesses

- Occasionally, histologic features are nonspecific (superficial perivascular lymphocytes)

### ANCILLARY TESTS

- Granular IgA (and occasional C3 or IgM) in dermal papillae

### TOP DIFFERENTIAL DIAGNOSES

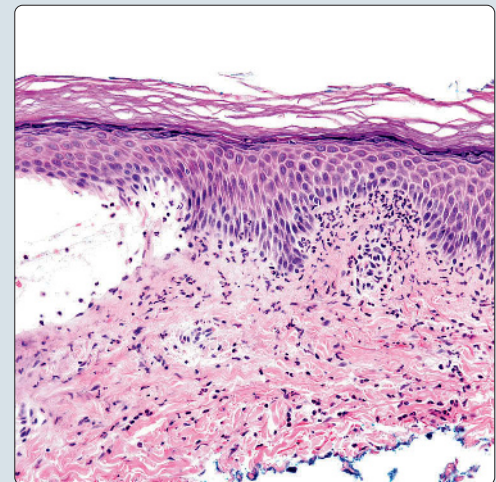
- Bullous pemphigoid
  - Tends to affect older individuals
  - Classically subepidermal split with prominent eosinophils
  - Direct immunofluorescence: Linear C3 and IgG
- Linear IgA disease/chronic bullous disease of childhood
  - Annular/polycyclic arrangements of tense bullae
  - Direct immunofluorescence: Linear IgA
- Cicatricial pemphigoid
- Bullous lupus erythematosus
- Epidermolysis bullosa acquisita

Erythematous Papules on Buttock

(Left) Intact vesicles are rarely seen in dermatitis herpetiformis as lesions are intensely pruritic. On the buttock, there are clustered erythematous papules that are slightly excoriated. (Right) In dermatitis herpetiformis, typically there is a subepidermal split with a predominance of neutrophils. Neutrophils are often clustered in adjacent dermal papillae.



Subepidermal Split With Neutrophils

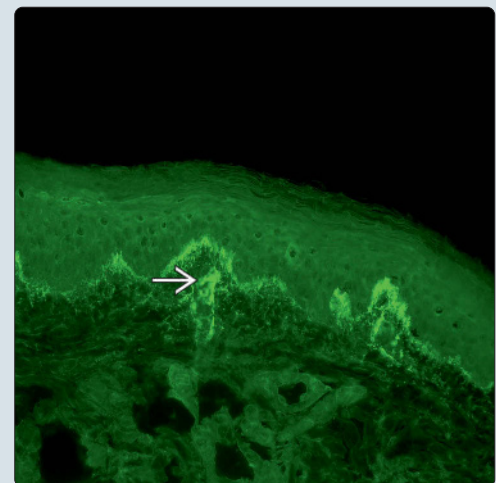


Neutrophils Within Dermal Papillae

(Left) Very early lesions of dermatitis herpetiformis may only show clusters of neutrophils in the dermal papillae. (Right) In dermatitis herpetiformis, the typical immunofluorescence pattern is granular IgA in the dermal papillae.



Granular IgA in Dermal Papillae (Direct Immunofluorescence)



## TERMINOLOGY

### Synonyms

- Duhring disease

### Definitions

- Subepidermal blistering disorder characterized by intense pruritus
- Highly associated with gluten-sensitive enteropathy

## ETIOLOGY/PATHOGENESIS

### At Least Partially Autoimmune

- Autoantibodies formed in gut cross react with epidermal transglutaminase

### Genetic Component

- Associated with *HLA-DQ2* and *DQ8*

## CLINICAL ISSUES

### Site

- Characteristically symmetrically involves elbows, knees, nape of neck, sacrum, scalp

### Presentation

- Vesicles rare, excoriations/erosions predominate
- Lesions grouped ("herpetiform")
- Rare urticarial/psoriasiform presentations

### Laboratory Tests

- Circulating autoantibodies
  - Against epidermal transglutaminase: Highly specific
  - Others include: Antitissue transglutaminase (antiendomysial), antigliadin, antireticulin

### Treatment

- Gluten-free diet
- Dapsone

### Disease Associations

- Gluten-sensitive enteropathy (often asymptomatic)
- Autoimmune thyroid disease
- Lymphoma of bowel

## MICROSCOPIC

### Histologic Features

- Early lesion
  - Papillary dermal microabscesses predominantly of neutrophils
- Later lesion
  - Subepidermal split with numerous neutrophils in base
  - Dermal papillae adjacent to split often contain microabscesses
- Occasionally, histologic features are nonspecific (superficial perivascular lymphocytes)

## ANCILLARY TESTS

### Immunofluorescence

- Granular IgA (and occasionally C3 or IgM) in dermal papillae
- Rare patterns
  - Linear IgA at dermal-epidermal junction

- Fibrillar IgA in dermal papillae

## DIFFERENTIAL DIAGNOSIS

### Bullous Pemphigoid

- Clinical
  - Tends to affect older individuals
  - Tense bullae
- Histopathological
  - Classically subepidermal split with prominent eosinophils
  - More rarely, neutrophils may predominate
  - Direct immunofluorescence: Linear C3 and IgG

### Linear IgA Disease/Chronic Bullous Disease of Childhood

- Clinical
  - Annular/polycyclic arrangements of tense bullae
- Histopathological
  - Subepidermal split with neutrophils
  - Direct immunofluorescence: Linear IgA

### Cicatricial Pemphigoid

- Clinical
  - Bullae with evidence of scarring
- Histopathological
  - Subepidermal split with mixed inflammatory infiltrate (sometimes neutrophils predominate)
  - Evidence of fibrosis
  - Direct immunofluorescence: Linear C3 and IgG as well as other immunoreactants

### Bullous Lupus Erythematosus

- Clinical
  - Patient with history/other findings of lupus erythematosus
- Histopathological
  - Subepidermal split with neutrophils
  - Direct immunofluorescence: Discontinuous deposition of C3, IgG, IgM, &/or IgA at dermal-epidermal junction

### Epidermolysis Bullosa Acquisita

- Clinical
  - Classically bullae on acral sites
  - Healing with milia
- Histopathological
  - Classically noninflammatory subepidermal split
  - Rarely is inflammatory with predominance of neutrophils

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Collections of neutrophils in papillary dermis
- In cases with subepidermal split, infiltrate is predominantly neutrophilic
- Granular IgA in dermal papillae on direct immunofluorescence

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# Cicatricial Pemphigoid

## KEY FACTS

### CLINICAL ISSUES

- 85% present with oral lesions and 25-30% with cutaneous lesions
- Erosive gingivitis, conjunctival erosions, and atrophic scarred cutaneous lesions
  - Erosive gingivitis involving gingiva, palate, buccal mucosa
- Potent topical steroids in gel, spray, mouthwash formulations for localized disease
- Systemic treatment (corticosteroids, steroid-sparing immunosuppression) for widespread disease
- Rituximab for advanced disease or severe new onset disease
- May be paraneoplastic

### MICROSCOPIC

- Subepidermal blister with neutrophils in blister space and mixed inflammatory infiltrate
- Older lesions demonstrate fibrosis

- Mucosal lesions present with plasma cells and occasional granulation tissue

### ANCILLARY TESTS

- Direct immunofluorescence of perilesional skin shows linear deposition of IgG &/or C3 at basement membrane zone, detectable in 80-90% of patients
- Indirect immunofluorescence microscopy using knockout skin substrate may help distinguish cicatricial pemphigoid from epidermolysis bullosa acquisita

### TOP DIFFERENTIAL DIAGNOSES

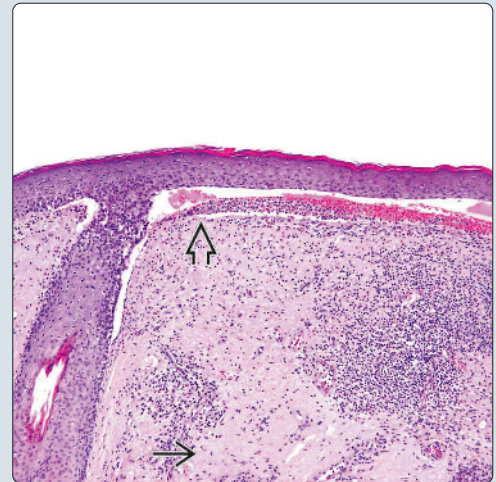
- Bullous pemphigoid
- Linear IgA bullous dermatosis
- Epidermolysis bullosa acquisita
- Pemphigus vulgaris

**(Left)** Clinical photograph of an African American patient shows cicatricial pemphigoid (CP) on the antecubital fossa of the forearm with a bulla [A], atrophic hypopigmented scarring [B], and hemorrhagic eschar [C]. **(Right)** Histologically, CP demonstrates a subepidermal blister [D] with a mixed dermal inflammatory infiltrate on the sides, base, and within the blister. Eosinophils were numerous on higher power. Note also the dermal fibrosis [E].

**Bulla, Scarring, and Eschar Formation**

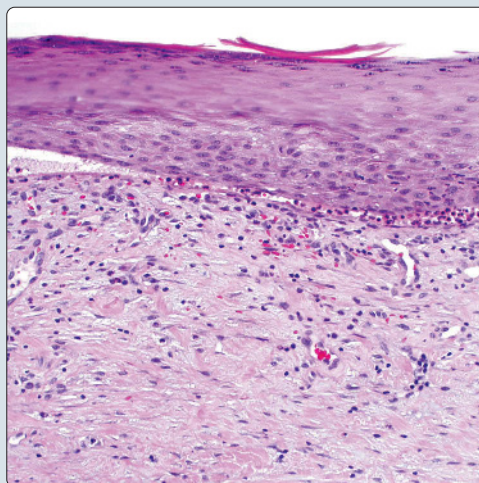


**Subepidermal Blister With Dermal Fibrosis and Eosinophils**

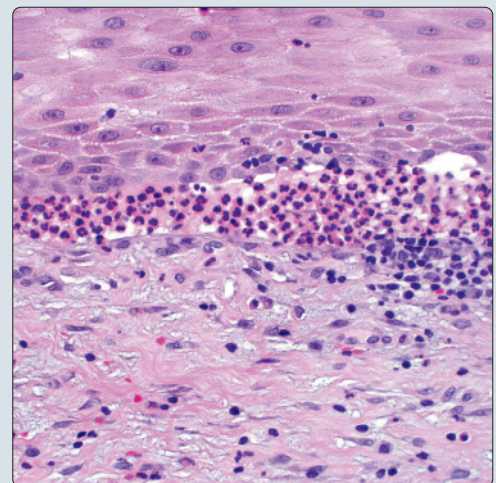


**Scarring in Cicatricial (Mucous Membrane) Pemphigoid**

**(Left)** Dermal fibrosis with vertically oriented vessels and effacement of rete characterize the scarring process of late stage cicatricial (mucous membrane) pemphigoid. **(Right)** Neutrophils are seen within a subepidermal vesicle overlying a fibrotic dermis.



**Neutrophils Within Subepidermal Vesicle in Cicatricial Pemphigoid**



## TERMINOLOGY

### Abbreviations

- Cicatricial pemphigoid (CP)

### Synonyms

- Mucous membrane pemphigoid, ocular pemphigoid, antiepiligrin CP, antilaminin-5 CP

### Definitions

- Scarring/blistering autoimmune disease of skin and mucosa
- Variants
  - Ocular variant with only conjunctival involvement; associated with  $\beta$ -4 integrin
  - Brunsting-Perry pemphigoid variant with localized cutaneous head and neck involvement; can lead to alopecia

## ETIOLOGY/PATHOGENESIS

### Autoimmunity

- Antibodies against C terminus of BPAG2 (BP180, collagen XVII), antilaminin 332 (epiligrin, laminin 5), or  $\beta$ -4-integrin (ocular variant)

### Malignancy

- Antilaminin-332 antibodies more commonly associated with malignancy, especially adenocarcinomas of lung and stomach

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - 1:1 million in Western Europe
- Age
  - Typically 60-80 years
- Sex
  - More common in women (1.5-2:1)
- Ethnicity
  - Association with *HLA-DQw7* (*HLA-DQB1\*0301*)

### Site

- Common cutaneous sites include scalp, face, neck, and trunk; result in atrophy and scarring
- Nasopharyngeal involvement may result in strictures, dysphagia, and airway obstruction
- Conjunctival involvement may lead to scarring, symblepharon, trichiasis, entropion, corneal ulceration, and eventual blindness
- Anal and genital involvement is rare

### Presentation

- 85% present with oral lesions and 25-30% with cutaneous lesions
- Erosive gingivitis involving gingiva, palate, buccal mucosa
- Intact bullae rare
- Chronic scarring may lead to adhesions and loss of teeth
- Ocular variant with only conjunctival involvement; associated with  $\beta$ -4-integrin
- Brunsting-Perry pemphigoid variant with localized cutaneous head and neck involvement; can lead to alopecia

## Treatment

- Surgical approaches
  - Tracheostomy for patients with severe esophageal stricture or nasopharyngeal involvement
  - Ophthalmological procedures for severe ocular scarring: Corneal grafts
- Drugs
  - Intralesional corticosteroid for localized disease
  - Systemic corticosteroids
  - Steroid-sparing agents
    - Tetracyclines, dapsone, cyclophosphamide, azathioprine, sulfapyridine, niacinamide, thalidomide, methotrexate
    - Dapsone may be used for oral and cutaneous lesions not responsive to topicals alone
    - Rituximab is emerging as first-line treatment for rapidly progressing disease
  - Topical therapy
    - Potent topical steroids in gel, spray, mouthwash formulations for localized disease, topical pimecrolimus/tacrolimus

## Prognosis

- Conjunctival involvement may lead to blindness
- Typically runs chronic course
- May lead to weight loss with nasopharyngeal involvement
- Higher mortality and morbidity with coexisting malignancy

## MACROSCOPIC

### General Features

- Erosive gingivitis, conjunctival erosions, and atrophic, scarred cutaneous lesions

## MICROSCOPIC

### Histologic Features

- Cutaneous CP
  - Subepidermal blister with inflammatory cells (neutrophils and eosinophils) in blister cavity, mixed perivascular infiltrate
  - Older lesions demonstrate fibrosis in dermis
  - Resembles cell-poor bullous pemphigoid
- Oral mucosal CP
  - Presents with plasma cells and occasional granulation tissue
  - Vesicle formation between stratified squamous mucosa and lamina propria
  - Edematous with mixed lymphocytes and histiocytes
- Conjunctival mucosal CP
  - Squamous metaplasia with hyperkeratosis, parakeratosis, loss of goblet cells, and mixed inflammatory infiltrate
  - Granulation tissue is present early, with scarring and fibrosis present in later lesions
- Laryngeal, esophageal, pharyngeal CP
  - Subepidermal bullae occasionally
  - Most commonly presents with erosions, ulcerations, and fibrosis that is nonspecific
  - Occasional stenosis

**ANCILLARY TESTS****Immunohistochemistry**

- Immunoblotting and immunoprecipitation show heterogeneous autoantibodies in CP

**Immunofluorescence**

- Direct immunofluorescence (DIF) of perilesional skin
  - Linear deposition IgG, IgA, &/or C3 at basement membrane zone
  - DIF is positive in 80-90% of patients
- Indirect immunofluorescence detects mainly IgG autoantibodies in 20-30% of patients
  - Higher titers often suggest more severe presentation
  - Indirect immunofluorescence microscopy using knockout skin substrate may help distinguish CP from epidermolysis bullosa acquisita
- Salt-split skin: Less value in diagnosing CP
  - Autoantibodies bind commonly to both epidermal and dermal fragment

**Serologic Testing**

- ELISA has high sensitivity and specificity for detecting autoantibodies in CP and may have prognostic value

**Electron Microscopy**

- Immunoelectron microscopy may help differentiate CP from other entities when DIF and indirect immunofluorescence (IIF) are negative or equivocal

**DIFFERENTIAL DIAGNOSIS****Histological**

- Bullous pemphigoid
  - Subepidermal bullae with eosinophils and lack of dermal fibrosis
- Linear IgA
  - Subepidermal bullae with abundance of neutrophils, eosinophils, and lymphocytes
    - Neutrophils often predominate
  - DIF shows linear IgA at dermal-epidermal junction
    - Linear IgG or C3 should be negative
  - Ocular lesions histologically indistinguishable from CP
- Pemphigus
  - Suprabasilar acantholysis
- Epidermolysis bullosa acquisita
  - Subepidermal bullae with paucicellular inflammation, blister may contain neutrophils
  - IIF on salt-split skin with linear deposition of antibodies at floor of blister

**Clinical**

- Bullous pemphigoid
  - Urticarial lesions and tense bulla
- Drug-induced bullous pemphigoid
  - History of drug exposure
  - Causative drugs include diuretics (furosemide), captopril, D-penicillamine, antibiotics (amoxicillin), gold, potassium iodide
- Epidermolysis bullosa acquisita
  - Tense vesicles and bullae
  - Presence of milia

- More recalcitrant to therapy than bullous pemphigoid
- Salt-split skin necessary to distinguish from bullous pemphigoid
- Linear IgA bullous dermatosis
  - Lesions often clustered in rosette or crown of jewels pattern
- Pemphigus vulgaris
  - Cutaneous erosions and flaccid bullae with oral ulcerative lesions
  - Easily distinguished from CP by routine H&E and DIF
- Erosive lichen planus
  - White streaks (Wickham striae)
  - May be more commonly associated with hepatitis C
- Chronic infectious conjunctivitis
  - May be difficult to distinguish from pure ocular CP
- Ocular pseudopemphigoid
  - Due to topical ophthalmologic medications, including pilocarpine,  $\beta$ -blockers, or idoxuridine
  - Self-limiting unilateral scarring from long-term eyedrops
- Late-stage Stevens-Johnson syndrome, toxic epidermal necrolysis
  - Often with inciting drug history
  - Often with associated extensive cutaneous lesions and desquamation

**DIAGNOSTIC CHECKLIST****Clinically Relevant Pathologic Features**

- Subepidermal bullae with superficial dermal fibrosis and plasma cells for mucosal lesions
- Presence of conjunctival scarring may indicate early symblepharon formation and future risk of blindness

**Pathologic Interpretation Pearls**

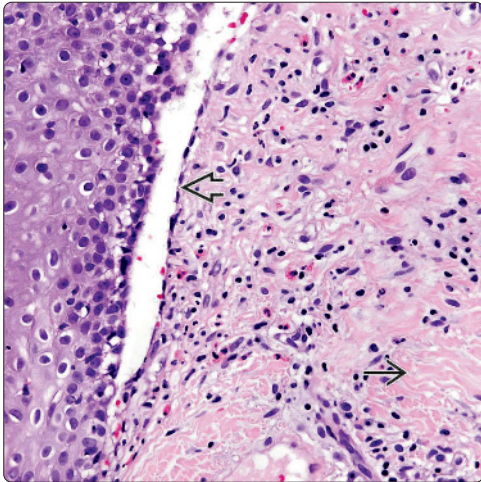
- Subepidermal bullae and presence of fibrosis
- Presence of granulation tissue in early lesions on mucosal sites

**SELECTED REFERENCES**

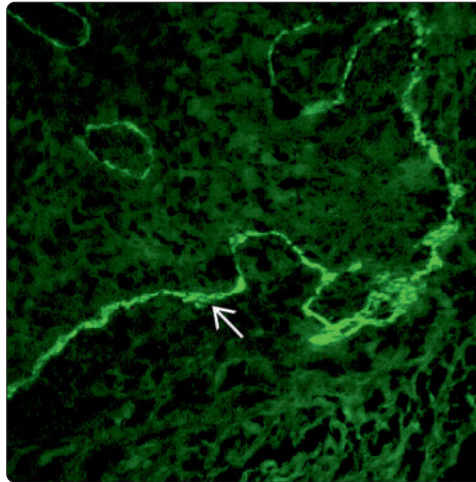
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**Subepidermal Split With Fibrosis and Mixed Dermal Infiltrate**

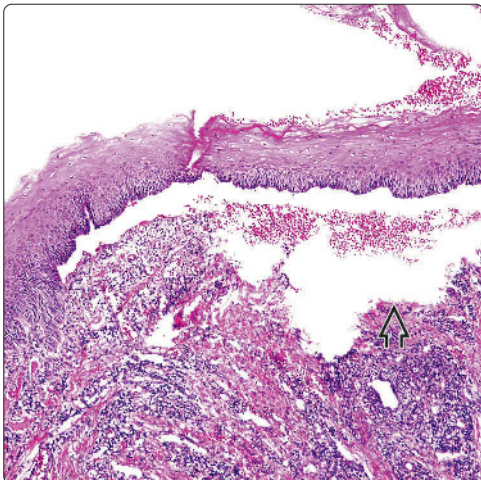


**Linear IgG at Dermal-Epidermal Junction on Direct Immunofluorescence**

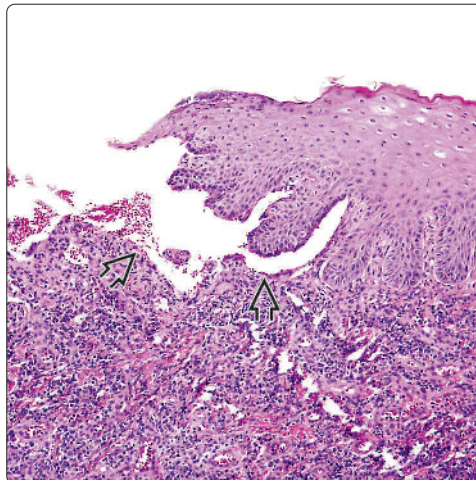


(Left) High-power view of CP from the edge of a hair follicle shows a split [arrowhead] between the follicle and adjacent dermis, which is a helpful clue in scalp biopsy specimens when CP may not be suspected clinically. There is a mixed dermal inflammatory infiltrate with accompanying fibrosis [arrow]. (Right) Direct immunofluorescence of CP displays the linear deposition of IgG at the dermal-epidermal junction [arrow].

**Subepidermal Blister of Mucosal Cicatricial Pemphigoid**

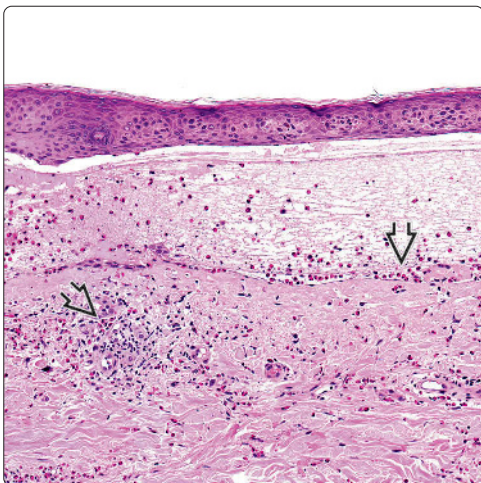


**Subepidermal Mucosal Blister With Lymphocytes and Plasma Cells**

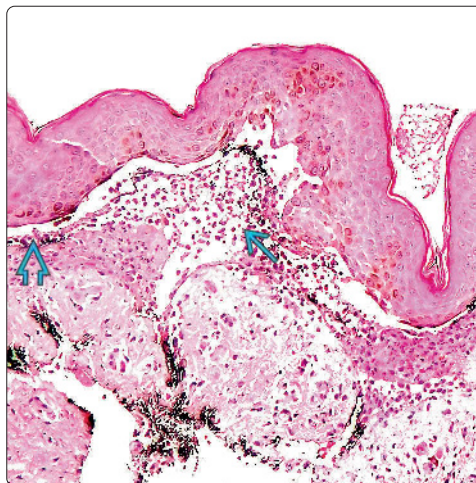


(Left) Mucosal CP demonstrates a subepidermal blister [arrowhead] and a dermal infiltrate containing numerous lymphocytes, plasma cells, rarer eosinophils, and occasional neutrophils. (Courtesy G. Ellis, DDS.) (Right) Mucosal CP on higher power demonstrates a dermal infiltrate composed mainly of lymphocytes and plasma cells underneath a subepidermal bulla [arrow]. (Courtesy G. Ellis, DDS.)

**Subepidermal Bulla With Eosinophils in Bullous Pemphigoid**



**Subepidermal Bulla of Linear IgA With Neutrophils**



(Left) Characteristic biopsy specimens of bullous pemphigoid demonstrate numerous eosinophils [arrow] within a subepidermal bulla, as well as within the superficial dermal inflammatory infiltrate. (Courtesy B. Ruben, MD.) (Right) Linear IgA typically demonstrates a subepidermal bulla [arrowhead] often with a dense neutrophilic infiltrate [arrow]. Direct immunofluorescence demonstrated linear IgA at the dermal-epidermal junction. (Courtesy P. Sarantopoulos, MD.)



# Hailey-Hailey Disease

## KEY FACTS

### ETIOLOGY/PATHOGENESIS

- Autosomal dominant genodermatosis
- Defects in *ATP2C1* gene

### CLINICAL ISSUES

- Typically affects intertriginous areas
- Erythematous, well-demarcated plaques, often crusted
- Malodor common

### MICROSCOPIC

- Extensive epidermal acantholysis
- Involves 1/2 or more of epidermis
- So-called dilapidated brick wall appearance
- Epidermis often hyperplastic
- Dyskeratosis with corp ronds may be evident but do not predominate
- Suprabasal clefting may be present

### TOP DIFFERENTIAL DIAGNOSES

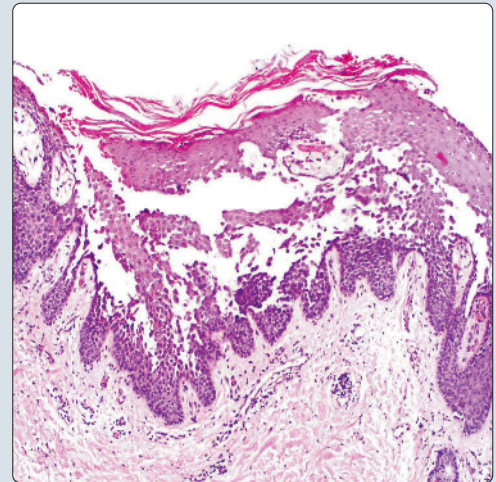
- Pemphigus vulgaris
  - Characteristic suprabasilar acantholysis without full-thickness epidermal involvement
- Acantholytic dermatosis of genitocrural area
  - May show identical features to Hailey-Hailey disease
  - Clinicopathologic correlation necessary for diagnosis
- Acantholytic acanthoma
  - Solitary papule/plaque
  - May show identical features to Hailey-Hailey disease
- Grover disease
  - 1-4 mm scaly erythematous papules on trunk
  - Foci of acantholysis are narrow, spanning no more than several rete
  - Spongiosis with dermal eosinophils
- Incidental histopathologic finding

**Crusted Erythematous Plaque**

**(Left)** Hailey-Hailey disease presents as erythematous plaques that are often focally crusted with macerated scale. Typically, plaques are located in intertriginous areas. (Courtesy S. Dyson, MD.)  
**(Right)** An acanthotic epidermis is disrupted by acantholysis throughout most of its layers.

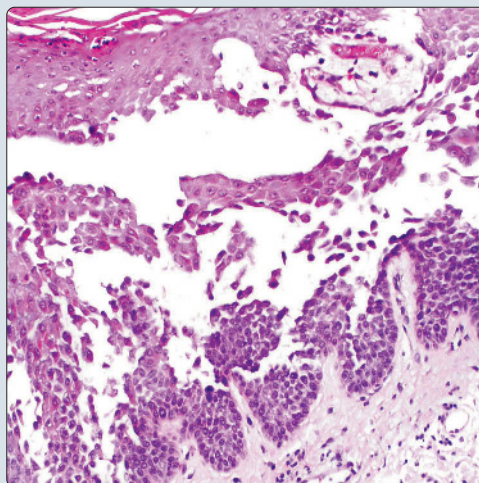


**Full-Thickness Acantholysis**

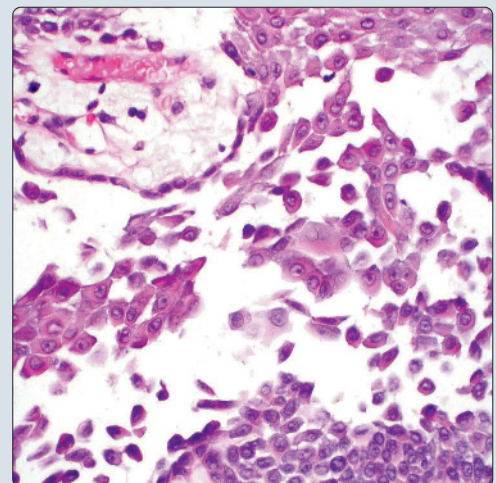


**Dilapidated Brick Wall Appearance**

**(Left)** Acantholysis creates an intraepidermal vesicle. Note how the acantholysis is involving more than 1/2 of the epidermis and it has the appearance of a dilapidated brick wall. **(Right)** In Hailey-Hailey disease, acantholytic keratinocytes lose their attachments to their neighbors and assume a rounded shape within the blister space.



**Acantholytic Keratinocytes**



## TERMINOLOGY

### Synonyms

- Familial benign chronic pemphigus

### Definitions

- Genodermatosis
- Intertriginous, erythematous plaques that characteristically show acantholysis on biopsy

## ETIOLOGY/PATHOGENESIS

### Genetic Basis

- Autosomal dominant
- Incomplete penetrance
- May be sporadic
- Defects in *ATP2C1* gene
  - Encodes calcium pump
  - Calcium is key factor in differentiation and adhesion of keratinocytes

## CLINICAL ISSUES

### Epidemiology

- Age
  - Generally presents in adolescence

### Site

- Typically affects intertriginous areas
  - Axillae
  - Inframammary
  - Perianal
  - Neck
- Unusual sites (e.g., face, scalp) have been reported

### Presentation

- Erythematous, well-demarcated plaques, often crusted
- Occasionally, bullae may be evident
- Plaques may be vegetative
- Malodor common
- Uncommon variants
  - Segmental/unilateral
- Lesions may be pruritic or burn

### Natural History

- Remissions and exacerbations common
- Exacerbating factors
  - Heat
  - Trauma
  - Moisture
  - Superinfection

### Treatment

- Topical agents
  - Corticosteroids
  - Antibiotics
  - Antifungals
  - Retinoids
- Oral agents (e.g., retinoids) for severe disease

## MICROSCOPIC

### Histologic Features

- Epidermal acanthosis with acantholysis
  - Involves 1/2 or more of epidermis (usually involves most levels of epidermis, extending from suprabasilar area to granular cell layer)
  - Epidermis often hyperplastic
  - So-called dilapidated brick wall appearance due to extensive acantholysis
  - Dyskeratosis with corp ronds may be evident but do not predominate
  - Suprabasal clefting may be present

## DIFFERENTIAL DIAGNOSIS

### Acantholytic Dermatitis of Genitocrural Area

- Clinical
  - Papules that may be confluent in genital area
- Histopathology
  - May show identical features to Hailey-Hailey disease
- Clinicopathologic correlation necessary for diagnosis

### Acantholytic Acanthoma

- Clinical
  - Solitary papule/plaque
  - Often on trunk
  - Generally biopsied to rule out malignancy or other keratinocytic neoplasm (e.g., basal cell carcinoma, inflamed keratosis)
- Histopathology
  - May show identical features to Hailey-Hailey disease

### Pemphigus Vulgaris

- Clinical
  - Typically presents with crusted erosions, including mucosal involvement
  - Often widespread
  - Nikolsky sign positive
- Histopathology
  - Characteristic suprabasilar acantholysis
  - Without full-thickness involvement of epidermis
  - Acantholysis extends down adnexal structures
- Direct immunofluorescence positive for intercellular epidermal network of C3 and IgG

### Grover Disease

- Clinical
  - 1-4 mm scaly erythematous papules on trunk
  - pruritic eruption, typically in elderly men
- Histopathology
  - May show acantholysis that is identical to Hailey-Hailey disease
  - Foci of acantholysis are narrow, spanning no more than several rete
  - Spongiosis with dermal eosinophils

## SELECTED REFERENCES

1. Engin B et al: Hailey-Hailey disease: a fold (intertriginous) dermatosis. Clin Dermatol. 33(4):452-5, 2015



# Epidermolysis Bullosa Acquisita

## KEY FACTS

### TERMINOLOGY

- Acquired epidermolysis bullosa

### ETIOLOGY/PATHOGENESIS

- Hepatitis C
- May be associated with other autoimmune or inflammatory diseases, including inflammatory bowel disease (Crohn), systemic lupus erythematosus (SLE), thyroid disease, diabetes, rheumatoid arthritis

### CLINICAL ISSUES

- Noninflammatory cutaneous vesicles and bullae, typically acral
- Lesions heal with atrophic scarring, milia, and hypopigmentation
- Severe cases may become mutilating with "mitten" deformities of hands and scarring alopecia
- Mucosal involvement may occur leading to dysphagia and esophageal stenosis

- Mechanobullae that develop with minimal friction in trauma-prone areas (e.g., hands, feet, elbows, knees)

### MICROSCOPIC

- Subepidermal bullae with either paucicellular or mixed inflammatory infiltrate


### ANCILLARY TESTS

- Salt-split skin linear deposition of antibodies at dermal side of cleavage (floor of blister)
- Direct immunofluorescence (DIF) of perilesional skin shows linear deposition of IgG at BMZ, occasionally linear C3, IgA, or IgM

### TOP DIFFERENTIAL DIAGNOSES

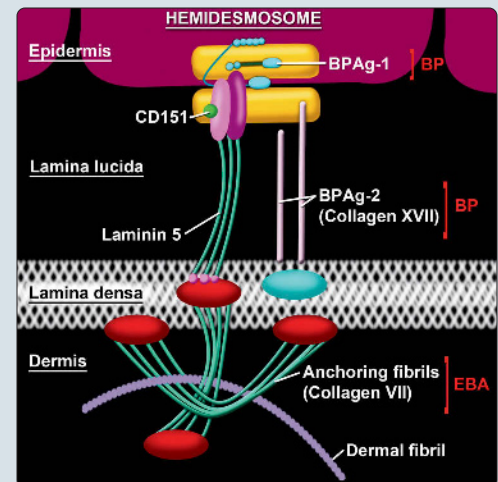
- Bullous pemphigoid
- Linear IgA
- Bullous SLE
- Dystrophic epidermolysis bullosa
- Porphyria cutanea tarda

### Acral Lesions of Epidermolysis Bullosa Acquisita

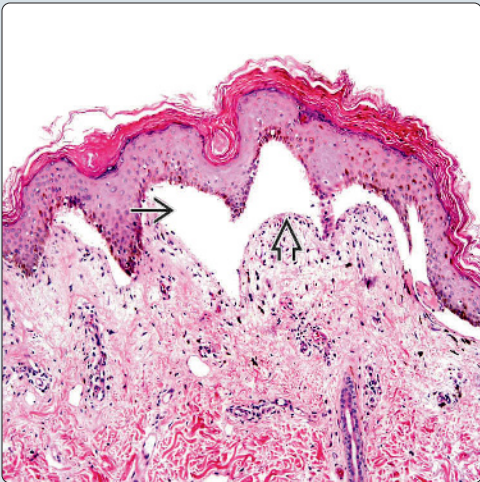



(Left) Epidermolysis bullosa acquisita (EBA) clinically displays characteristic erosions . Intact bullae and milia (not shown) can also be present. (Courtesy Victor D. Newcomer Collection at UCLA and Logical Images, Inc.) (Right) Illustration of the components of the dermal-epidermal junction zone demonstrates the important adhesion molecules. BP has antibodies to BPAg-1 and BPAg-2. EBA has antibodies to anchoring fibrils (collagen VII). Inherited epidermolysis bullosa is caused by abnormal anchoring fibrils.

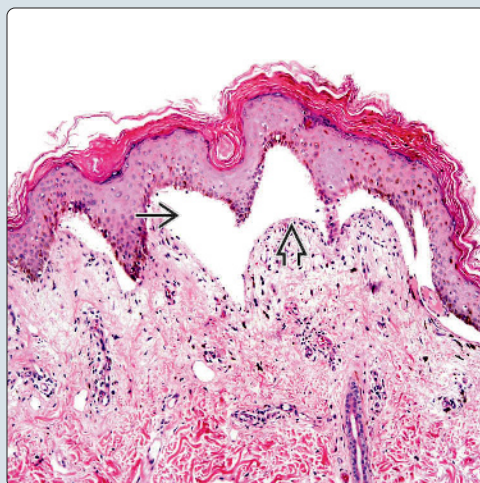


### Basement Membrane Proteins

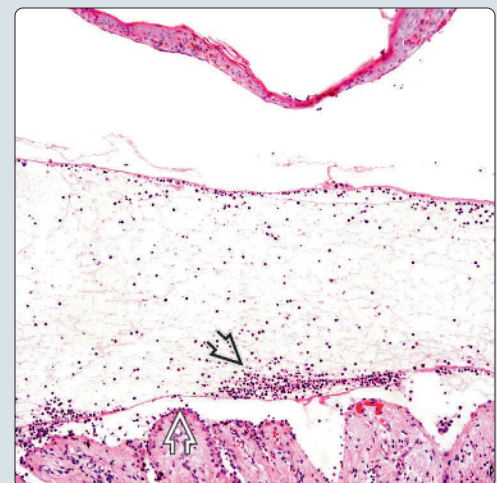


### Paucicellular Subepidermal Blister of Epidermolysis Bullosa Acquisita

(Left) This example of EBA demonstrates a subepidermal bulla  with an almost complete absence of inflammatory cells (paucicellular infiltrate) within the blister cavity . (Right) High-power view of another lesion of EBA demonstrates scattered groups of acute and chronic inflammatory cells  within a subepidermal bulla .



### Mixed Acute and Chronic Inflammation



## TERMINOLOGY

### Abbreviations

- Epidermolysis bullosa acquisita (EBA)

### Synonyms

- Acquired epidermolysis bullosa

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- Hepatitis C

### Autoimmunity

- May be associated with other autoimmune or inflammatory diseases, including inflammatory bowel disease (Crohn), systemic lupus erythematosus (SLE), thyroid disease, diabetes, rheumatoid arthritis

### Neoplasms

- Gynecological (uterine, cervical, ovarian)
- Multiple myeloma

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - 0.25 cases per 1 million per year
- Age
  - Any, although more common in adults

### Presentation

- Noninflammatory cutaneous vesicles and bullae, typically acral
- Mechanobullae that develop with minimal friction in trauma-prone areas (e.g., hands, feet, elbows, knees)
- Lesions heal with atrophic scarring, milia, and hypopigmentation
- Severe cases may become mutilating with "mitten" deformities of hands and scarring alopecia
- Mucosal involvement may occur leading to dysphagia and esophageal stenosis

### Treatment

- Drugs
  - Systemic corticosteroids
  - Steroid-sparing agents
    - Azathioprine, methotrexate, cyclophosphamide, colchicine, dapsone, gold, cyclosporine

### Prognosis

- If paraneoplastic, often responds to adequate treatment of underlying malignancy
- Other variants are often refractory to treatment

## MACROSCOPIC

### General Features

- Mechanobullae typically acral in distribution with milia and atrophic scarring

## MICROSCOPIC

### Histologic Features

- Subepidermal cleft or bullae with either paucicellular inflammatory infiltrate or mixed inflammatory infiltrate composed of neutrophils, eosinophils, lymphocytes

## ANCILLARY TESTS

### Immunofluorescence

- Direct immunofluorescence (DIF) of perilesional skin shows linear deposition IgG at basement membrane zone, occasionally linear C3, IgA, or IgM may be present
- Indirect immunofluorescence with salt-split skin detects circulating IgG to Collagen VII in patient's serum in ~ 50% of patients with EBA
  - Bullous pemphigoid: Immune deposits bind to roof of blister
  - EBA: Immune deposits bind to floor of blister

### Serologic Testing

- ELISA: Sensitive test, detects serum IgG to anchoring fibrils

## DIFFERENTIAL DIAGNOSIS

### Histological and Clinical Differential Diagnoses

- **Bullous pemphigoid**
  - Subepidermal bullae with abundance of eosinophils
  - IIF with salt-split skin shows linear deposition of antibodies at roof of blister
- **Linear IgA**
  - Subepidermal bullae with abundance of neutrophils
  - DIF shows linear deposition of IgA at dermal-epidermal junction (DEJ)
- **Bullous systemic lupus erythematosus**
  - May also have circulating antibodies to anchoring fibrils type VII collagen
  - Subepidermal bullae with abundance of neutrophils, perivascular and periadnexal lymphocytic infiltrate, interface changes, and mucin
  - DIF: Linear and granular IgG and C3 at DEJ
- **Cicatricial pemphigoid**
  - Subepidermal bullae with dermal fibrosis
  - DIF with linear deposition of IgG at DEJ
- **Inherited dystrophic epidermolysis bullosa**
  - Most closely resembles mechanobullous form of EBA
  - Distinguish by lack of family history and DIF findings in EBA
- **Porphyria cutanea tarda (PCT)**
  - Mimics EBA with prominent acral involvement
  - Porphyrin studies can distinguish PCT from EBA
- **Pseudoporphyria**
  - Thorough drug history may be necessary to help distinguish from EBA

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# Epidermolysis Bullosa (Inherited)

## KEY FACTS

### TERMINOLOGY

- Heterogeneous group of noninflammatory inherited disorders characterized by development of blisters or erosions after minor trauma

### ETIOLOGY/PATHOGENESIS

- Autosomal dominant or recessive

### CLINICAL ISSUES

- 50 per 1 million live births
  - 92% epidermolysis bullosa (EB) simplex
- Symptomatic treatment
- **EB simplex:** Generally mild, blisters heal without scarring
  - Mostly autosomal dominant
  - Recessive forms tend to be more severe
- **Junctional EB:** Very rare, autosomal recessive
- **Dystrophic EB:** Trauma-induced blisters that heal with scarring

### MICROSCOPIC

- All forms in routine histology generally show cell-poor subepidermal blister
- Immunofluorescence (or immunohistochemistry) may help subclassification
- Biopsy from edge of fresh blister

### ANCILLARY TESTS

- Antibody mapping of basement membrane zone most useful, performed at specialized laboratories

### TOP DIFFERENTIAL DIAGNOSES

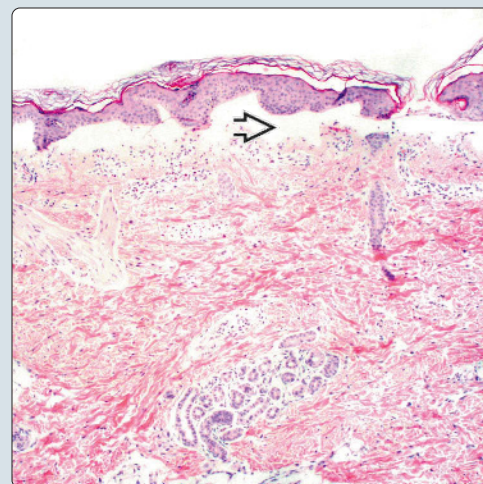
- Porphyria cutanea tarda
- Bullous pemphigoid
- Toxic epidermal necrolysis

#### Blisters, Erosions, and Loss of Toenails

(Left) This clinical photo of dystrophic epidermolysis bullosa (EB) shows blisters, erosions, and loss of toenails. (Right) Low-power view of EB shows a subepidermal split with an unremarkable underlying dermis.



#### Subepidermal Split

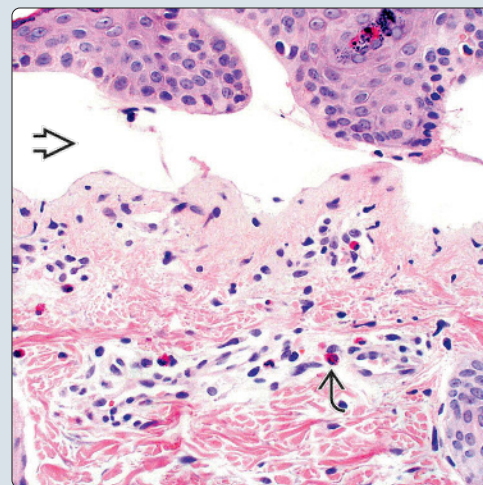


#### Scarring With Early Mitten Deformity

(Left) This infant with dystrophic EB has scarring with early mitten deformity (indicated by a black arrow). (Right) This high-power view of epidermolysis bullosa shows scattered eosinophils (indicated by a black arrow) in the dermis underlying a subepidermal split (indicated by a black arrow). Eosinophils can be seen in some subtypes of EB but are not really useful in subclassification.



#### Subepidermal Split With Occasional Eosinophils





## TERMINOLOGY

### Abbreviations

- Epidermolysis bullosa (EB)

### Definitions

- Heterogeneous group of noninflammatory inherited disorders characterized by development of blisters or erosions after minor trauma

## ETIOLOGY/PATHOGENESIS

### Inherited

- Autosomal dominant or recessive
- Basement membrane zone is composed of numerous specialized components that are defective in EB
  - Basal cell cytoskeleton
  - Anchoring filaments
  - Collagen fibrils
- **EB simplex**
  - Mutations in CK5, CK14
- **Junctional EB**
  - Mutations in laminin 5, CD103, type XVII collagen
- **Dystrophic EB**
  - Mutations in type VII collagen gene

### Acquired

- Autoimmune

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - 50 per 1 million live births
  - 92% EB simplex
- Sex
  - M:F = 1:1
- Ethnicity
  - No predilection

### Epidermolysis Bullosa Simplex

- Generally mild, blisters heal without scarring
  - No to mild internal involvement
- Mostly autosomal dominant
- Recessive forms tend to be more severe

### Junctional Epidermolysis Bullosa

- Very rare, autosomal recessive
- Blisters heal usually without scarring

### Dystrophic Epidermolysis Bullosa

- Trauma-induced blisters that heal with scarring
- Nail dystrophy, mucosal and GI lesions, aplasia cutis, anemia

## MACROSCOPIC

### General Features

- Superficial blisters present as crusted erosions
- Intraepidermal blisters are flaccid, may expand with pressure
- Blisters within lamina lucida are tense, heal with atrophy but without scarring
- Sublaminal blisters heal with scarring and milia formation

## MICROSCOPIC

### Histologic Features

- All forms in routine histology generally show cell-poor subepidermal blister
  - Most useful for ruling out other causes of blistering
- Immunofluorescence (or immunohistochemistry) may help subclassification

### Specimen Requirements

- Biopsy from fresh blister
  - Create blister in clinic
  - Blisters already present in clinic that appear fresh may have early reepithelialization that would make classification impossible
- 2 (or 3) biopsy specimens
  - 1 for routine histochemistry
  - 1 for immunofluorescence
  - Possibly 1 for electron microscopy
- Take biopsy from edge of blister
- Do not bisect biopsy!
  - Excess handling can create artifactual cleavage planes, making interpretation difficult

## ANCILLARY TESTS

### Immunofluorescence

- Absent or altered staining patterns can indicate specific molecular defect
- Antibody mapping of basement membrane zone most useful
  - Performed at specialized laboratories

## DIFFERENTIAL DIAGNOSIS

### Porphyrria Cutanea Tarda

- Blisters in light-exposed areas, especially dorsum of hands
- Subepidermal blister with preservation of dermal papillae

### Bullous Pemphigoid

- Usually has dermal inflammatory infiltrate

### Toxic Epidermal Necrolysis

- Severe form of erythema multiforme
- Necrosis of overlying epidermis

### Burn

- Overlying dermis necrotic

### Drug Reaction

- Uncommon
- Inflammatory infiltrate variable

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3. Bchetnia M et al: Expression signature of epidermolysis bullosa simplex. *Hum Genet*. 131(3):393-406, 2012
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# Linear IgA Bullous Dermatitis

## KEY FACTS

### TERMINOLOGY

- Rare autoimmune or drug-induced bullous disease with continuous linear IgA deposits along basement membrane zone on direct immunofluorescence (DIF)

### CLINICAL ISSUES

- Classically tense vesicles and bullae, erythematous patches, and occasional erosions on trunk and extremities
  - Occasionally annular blisters form, producing rosette or cluster of jewels appearance

### MICROSCOPIC

- Subepidermal blisters often with numerous neutrophils &/or eosinophils
  - Superficial perivascular lymphocytic infiltrate and basal cell vacuolization
- Features are largely nonspecific and can mimic other blistering diseases
  - DIF is necessary for diagnosis

### ANCILLARY TESTS

- DIF
  - By definition shows linear IgA at dermal-epidermal junction in all cases
  - Possibly faint deposits of IgG, IgM, and complement
- Salt-split skin preparation
  - IgA stains positive in roof of blister (combined dermal staining may also be present)

### TOP DIFFERENTIAL DIAGNOSES

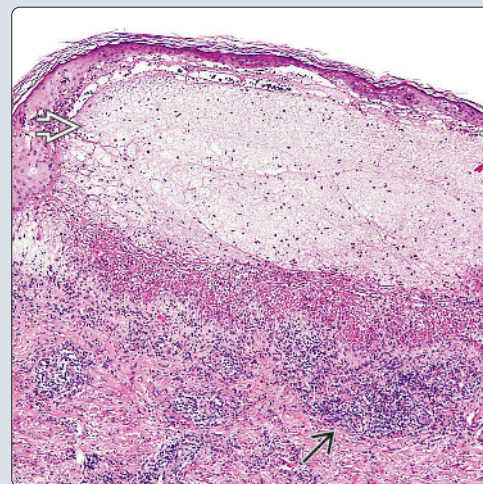
- Dermatitis herpetiformis
  - DIF: Granular deposition of IgA in dermal papillae
- Bullous pemphigoid
  - DIF shows linear deposition of IgG &/or C3 at basement membrane zone
- Bullous lupus erythematosus
  - DIF: IgG  $\pm$  IgA and IgM at basement membrane

**Tense Vesicles and Bullae**

(Left) Classically, linear IgA bullous dermatosis (LABD) presents as tense vesicles and bullae, erythematous patches, and occasional erosions on the trunk as seen in this patient. Annular blisters may also form, creating a cluster of jewels appearance. (Right) LABD demonstrates a subepidermal blister filled with some acute and chronic inflammatory cells with a superficial perivascular lymphocytic infiltrate.

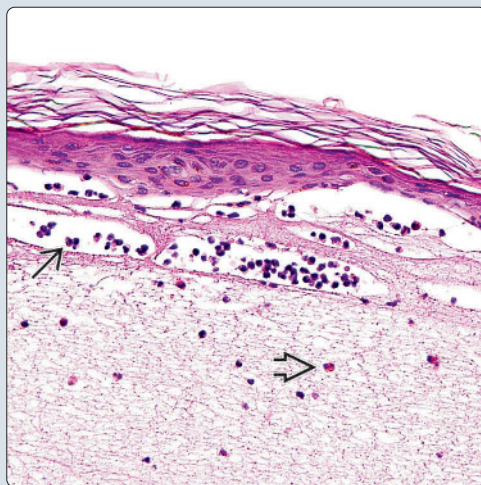


**Subepidermal Blister With Mixed Inflammation**

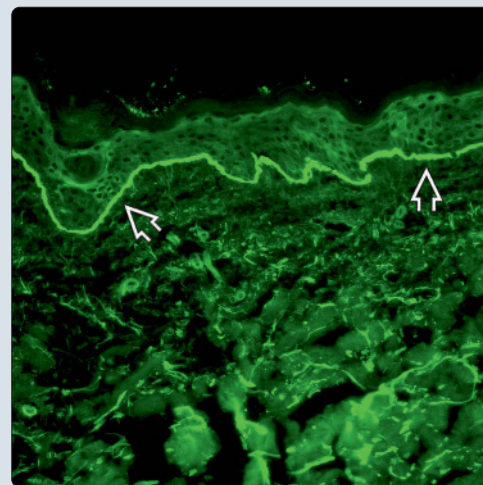


**Blister With Neutrophils and Eosinophils**

(Left) High-power view shows that the blister cavity is filled with neutrophils and occasional eosinophils. (Right) Direct immunofluorescence of an LABD lesion shows characteristic continuous linear IgA deposition along the dermal-epidermal junction. (Courtesy K. Leiferman, MD.)



**DIF With Linear IgA Deposition Along Dermal-Epidermal Junction**





## TERMINOLOGY

### Abbreviations

- Linear IgA bullous dermatosis (LABD)

### Synonyms

- Chronic bullous disease of childhood, linear IgA disease, linear IgA dermatosis

### Definitions

- Rare autoimmune or drug-induced bullous disease with continuous linear IgA deposits along basement membrane zone (BMZ) on direct immunofluorescence (DIF)

## ETIOLOGY/PATHOGENESIS

### Autoimmune Disease

- IgA autoantibodies typically directed against proteolytic fragment of BP180 antigen
- May be drug induced, systemic disease associated, or idiopathic
  - Drugs implicated include vancomycin (most common), NSAIDs (especially diclofenac), lithium, furosemide, others
  - Some cases associated with preceding infection

## CLINICAL ISSUES

### Epidemiology

- Age
  - Adults:  $\geq 60$  yr
  - Children: Mean is 4-5 yr
  - Drug-induced form more common in elderly adults
- Sex
  - M ~ F

### Presentation

- Classically tense vesicles and bullae, erythematous patches, and occasional erosions on trunk and extremities
  - Occasionally annular blisters form, producing rosette or cluster of jewels appearance
  - May progress to involve palms, soles, and mucous membranes
  - Rare morbilliform variant without blistering has been reported in drug-induced LABD

### Treatment

- Dapsone is drug of choice for idiopathic LABD
  - Colchicine, sulfapyridine, or systemic corticosteroids can be used if dapsone is ineffective or not tolerated
- If drug induced, removal of offending agent quickly resolves lesions (in  $< 3$  weeks)

### Prognosis

- In children, disease remits within 2 yr in  $> 50\%$  of patients
- Remission less common in adults with average duration of 10 yr

## MICROSCOPIC

### Histologic Features

- Largely nonspecific and can mimic other blistering diseases
  - DIF is necessary for diagnosis

- Subepidermal blisters often with numerous neutrophils &/or eosinophils
  - Often superficial perivascular lymphocytic infiltrate occasionally with eosinophils and basal cell vacuolization
- Microabscesses may form at dermal papillary tips, similar to dermatitis herpetiformis
- Rarely, blister cavity is paucicellular

## ANCILLARY TESTS

### Immunofluorescence

- DIF
  - By definition shows linear IgA at dermal-epidermal junction in all cases
    - Possibly faint deposits of IgG, IgM, and complement
- Indirect immunofluorescence (IIF)
  - Serum epithelial BMZ IgA antibodies positive in 60-70% of patients
    - In drug-induced LABD, antibodies often absent

### Salt-Split Skin Preparation

- IgA stains positive in roof of blister (combined dermal staining may also be present)

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Dermatitis herpetiformis
  - Collections of neutrophils in dermal papillae
  - DIF: Granular deposition of IgA in dermal papillae
- Bullous pemphigoid
  - Symmetrical pruritic vesicle and tense bullae
  - Subepidermal blister with numerous eosinophils
  - DIF shows linear deposition of IgG &/or C3 at BMZ
- Bullous lupus erythematosus (LE)
  - Acquired tense, vesicobullous eruption arising in patients with systemic LE
  - DIF: IgG  $\pm$  IgA and IgM at basement membrane

### Clinical

- Bullous pemphigoid
- Dermatitis herpetiformis
- Pemphigus
  - Painful, flaccid blisters or erosions (blisters rare)
  - Characteristic histology of suprabasal blister gives basal cells tombstone appearance
  - DIF: Intercellular IgG/IgA in chicken-wire pattern
- Cicatricial pemphigoid
  - Typically affects mucous membranes and conjunctiva; rare cutaneous involvement
  - DIF shows linear deposition of IgG &/or C3 along basement membrane
- Bullous impetigo (especially in young children)
  - Favors moist, intertriginous areas, and often golden crust seen clinically
  - DIF negative, often gram-positive cocci on biopsy

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# Erythema Toxicum Neonatorum

## KEY FACTS

### TERMINOLOGY

- Benign, self-limited eruption in neonates

### CLINICAL ISSUES

- Affects 30-70% healthy term infants
  - Up to 5% of premature infants
- Presents within 1st few days of life
- Generally any hair-bearing area, especially trunk
- Erythematous macules, plaques, pustules
- Prognosis is excellent, resolves spontaneously

### MICROSCOPIC

- Subcorneal or intraepidermal pustules filled with eosinophils
- Eosinophilic infiltrate in upper dermis near follicles
- Smaller numbers of neutrophils and monocytes
- Increased mast cells around follicles
- Tzanck smear often performed for diagnosis

### TOP DIFFERENTIAL DIAGNOSES

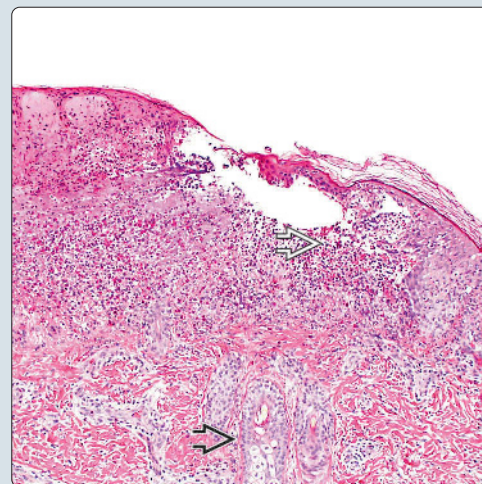
- Eosinophilic pustular folliculitis
  - Very similar histology with different clinical presentation
  - Chronic dermatosis with recurrent papules, pustules, and plaques
- Childhood eosinophilic folliculitis
  - Older children (not newborns)
  - Interfollicular rather than follicular
- Infectious folliculitis
  - Organisms apparent on special stains or positive culture
- Clinical differential diagnosis
  - Generalized herpes simplex virus
  - Infectious folliculitis
  - Drug eruption
  - Hand, foot, and mouth disease

**Yellow Plaque on Erythematous Base**

(Left) This clinical picture of erythema toxicum neonatorum (ETN) on the buttocks shows a yellow raised plaque over an erythematous base. (Right) Erythema toxicum of the newborn is a pustular lesion centered around hair follicles. Notice the eosinophil-filled pustule with an associated underlying follicle.

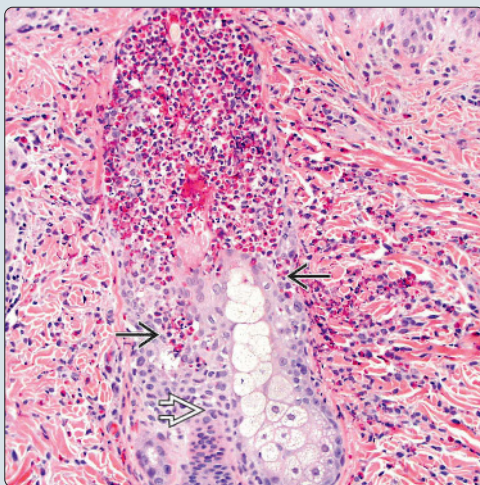


**Eosinophil-Filled Pustule**

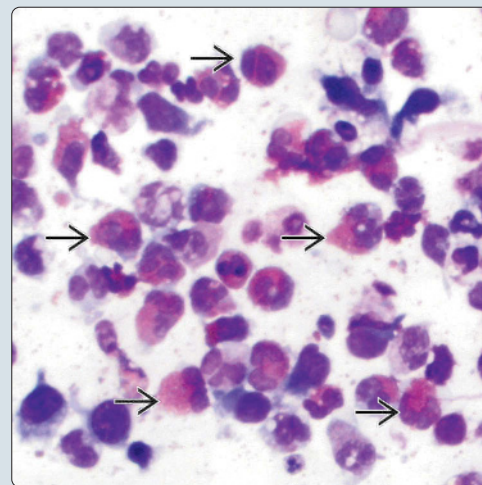


**Peri- and Intrafollicular Eosinophils**

(Left) ETN is a folliculocentric lesion. Eosinophils can be seen surrounding a hair follicle and invading the follicular epithelium. (Right) Tzanck smears are often performed to diagnose ETN. Numerous eosinophils are seen and should be > 90% of the total cell population.



**Numerous Eosinophils on Tzanck Smear**





## TERMINOLOGY

### Abbreviations

- Erythema toxicum neonatorum (ETN)

### Synonyms

- Erythema toxicum
- Toxic erythema of newborn

### Definitions

- Benign, self-limited eruption in neonates
- Common neonatal rash

## ETIOLOGY/PATHOGENESIS

### Unknown

- Presence of eosinophils suggests allergic or hypersensitivity reaction
- Increased inflammatory mediators suggest immune system response
- No organisms have been found to cause ETN
- Mechanical irritation has been ruled out as etiology
- No exotoxin or allergen has been found to cause ETN

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - 30-70% healthy term infants
  - Up to 5% of premature infants
    - Delayed onset more common in premature infants
- Age
  - 1st few days of life
  - Peaks at 48 hours
- Sex
  - Somewhat higher incidence in males
- Ethnicity
  - No predilection

### Site

- Generally any hair-bearing area
  - Trunk most common
- No mucosal, palmar, or plantar involvement
- Number and distribution vary widely

### Presentation

- Erythematous macules, plaques, pustules
- No systemic signs (e.g., fever)
- No maternal history of viral infection

### Laboratory Tests

- Eosinophilia seen in up to 15%

### Natural History

- Resolves within days with no sequelae

### Prognosis

- Excellent, resolves spontaneously
- Recurrences possible up to 6 weeks of age
  - Recurrences are mild

## MICROSCOPIC

### Histologic Features

- Subcorneal or intraepidermal pustules
  - Filled with eosinophils
  - Related to openings of pilosebaceous units
- Eosinophilic infiltrate in upper dermis near follicles
  - Smaller numbers of neutrophils and monocytes
- Intraepithelial eosinophils around follicles
- Increased mast cells around follicles

### Cytologic Features

- Tzanck smear often performed for diagnosis
- Inflammatory cells present with > 90% eosinophils
- Absence of viral inclusions

## DIFFERENTIAL DIAGNOSIS

### Eosinophilic Pustular Folliculitis

- Very similar histology with different clinical presentation
  - Chronic dermatosis with recurrent papules, pustules, and plaques

### Childhood Eosinophilic Folliculitis

- Older children (not newborns)
- Interfollicular rather than follicular

### Infectious Folliculitis

- Organisms apparent on special stains or positive culture

### Clinical Differential Diagnosis

- Generalized herpes simplex (HSV)
  - Clinically very sick/toxic infant
  - Positive Tzanck smear showing multinucleated giant cells (not eosinophils)
  - PCR, biopsy, or culture will help identify HSV
  - Important to rule out because can be fatal
- Infectious folliculitis
  - Culture helpful to rule out
  - Folliculitis uncommon in neonates
- Drug eruption
  - History of drug ingestion
  - Biopsy, smear would help delineate
- Hand, foot, and mouth disease
  - Clinically can look identical, but patient is usually febrile
  - Favors palms, soles, and mucous membranes (vs. ETN)
  - Usually affects young children (vs. neonates)
  - Caused by coxsackievirus

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Subcorneal or intraepidermal pustules filled with eosinophils
- Eosinophilic infiltrate in upper dermis near follicles
- Intraepithelial eosinophils around follicles

## SELECTED REFERENCES

1. Monteagudo B et al: Prospective study of erythema toxicum neonatorum: epidemiology and predisposing factors. *Pediatr Dermatol.* 29(2):166-8, 2012
2. Morgan AJ et al: Erythema toxicum neonatorum revisited. *Cutis.* 83(1):13-6, 2009

# Transient Neonatal Pustular Melanosis

## KEY FACTS

### CLINICAL ISSUES

- Benign, self-limited dermatosis
- Most commonly occur in African American infants (~ 4-5%) with no gender predilection
- Lesions are apparent at birth or develop over first 24 hours of life
- Small vesicopustules with nonerythematous base
- Treatment is often unnecessary

### MICROSCOPIC

- Subcorneal pustules containing neutrophils and occasional eosinophils
- Intracorneal neutrophilic infiltrate
- Dermis is usually uninvolved
- Tzanck smear may show neutrophils ± eosinophils

### ANCILLARY TESTS

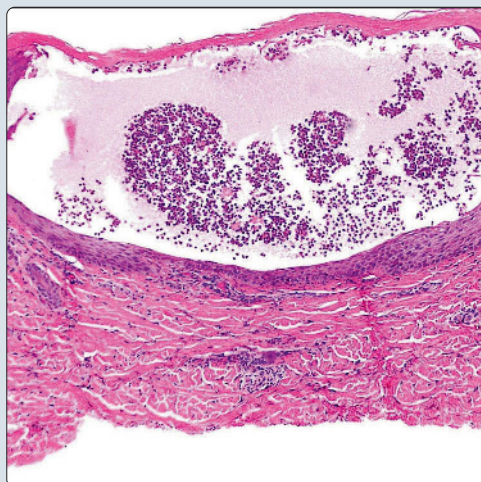
- Direct and indirect immunofluorescence is negative for deposits of antibody and complement

### TOP DIFFERENTIAL DIAGNOSES

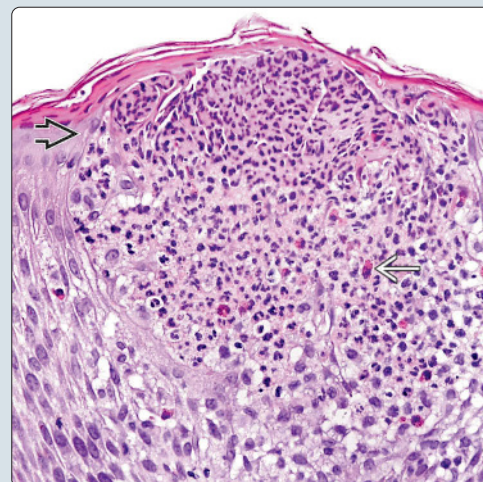
- Infections
  - Ancillary studies, such as Gram stain, GMS stain, and cultures of lesions, as well as serological examination and complete blood count assist with final diagnosis
- Acropustulosis of infancy
  - Histologic findings overlap with those seen in transient neonatal pustular melanosis
- Erythema toxicum neonatorum
  - Histologic examination shows eosinophilic folliculitis and subcorneal eosinophilic pustules
- Eosinophilic pustular folliculitis of infancy
  - Histologic examination shows eosinophilic spongiosis and mixed perifollicular inflammatory infiltrate
- Langerhans cell histiocytosis
  - Histologic examination shows infiltrate of Langerhans cells [CD1a and S100 (+)]

(Left) Scanning view of transient neonatal pustular melanosis (TNPM) demonstrates neutrophil infiltrations in intracorneal and subcorneal layers. Although neutrophils are the predominant inflammatory cell seen in TNPM, pustules in TNPM can sometimes contain eosinophils. (Right) Biopsy of TNPM shows a subcorneal pustule [ ] containing predominantly neutrophils and a few eosinophils [ ].

Intracorneal Blister With Neutrophils

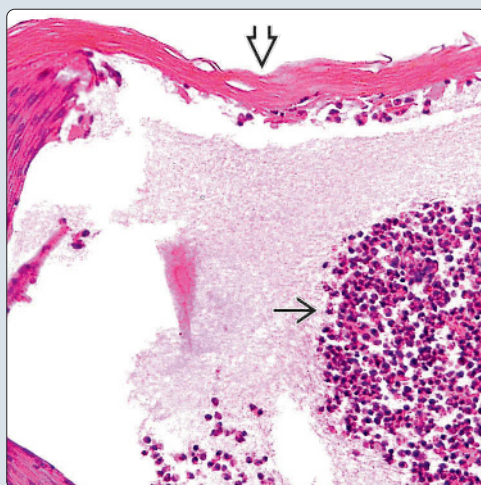


Subcorneal Pustule With Neutrophils and Occasional Eosinophils

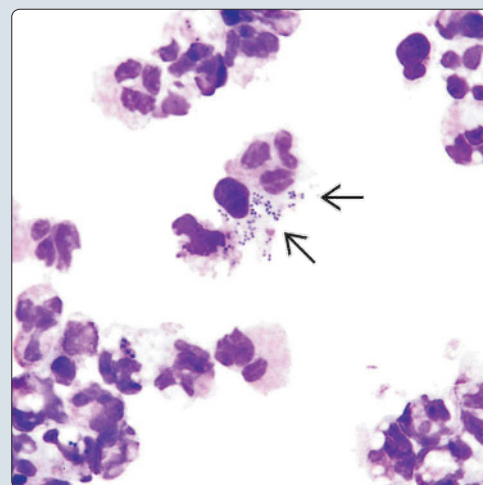


(Left) In acropustulosis of infancy, the subcorneal pustule [ ] contains numerous eosinophils [ ], which may be admixed with a variable amount of neutrophils. (Courtesy M. Chaffins, MD.) (Right) Both bacterial infection and TNPM show neutrophils at Tzanck smear. In this case, intracellular cocci are identified [ ], consistent with infection.

Subcorneal Pustule With Numerous Eosinophils in Acropustulosis of Infancy



Intracellular Cocci in Tzanck Smear Indicating Infection



## TERMINOLOGY

### Abbreviations

- Transient neonatal pustular melanosis (TNPM)

### Synonyms

- Transient neonatal pustulosis
- Lentiginis neonatorum

## ETIOLOGY/PATHOGENESIS

### Etiology

- Unknown
- No correlation with infection or drug exposure

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - **Most commonly occurs in African American infants (~4-5%)**
  - Overall incidence is 0.2%
    - Affects ~ 0.6% of Caucasian infants
    - Rare in Asians
- Sex
  - No gender predilection

### Site

- Scalp often spared
- Usually affects face, neck, trunk, thighs, buttock, palms, soles

### Presentation

- Small vesicopustules with **nonerythematous base**
- Vesicopustules resolve spontaneously, leaving hyperpigmented macules
- Vesiculopustular stage may occur in utero, with only hyperpigmented macules seen after birth
- Not associated with systemic manifestations

### Laboratory Tests

- Complete blood count may show eosinophilia

### Natural History

- Vesicopustules &/or hyperpigmented macules are apparent at birth or develop over first 24 hours of life
- Vesicles rupture shortly after eruption
- Healed lesions show hyperpigmentation with surrounding scaly collarettes
- Complete resolution is achieved within weeks
- Lesions in TNPM do not tend to recur

### Treatment

- Often unnecessary

### Prognosis

- Benign, self-limited dermatosis

## MICROSCOPIC

### Histologic Features

- Subcorneal pustules containing neutrophils and occasional eosinophils
- Intracorneal neutrophilic infiltrate

- Dermis is usually uninvolved
  - Late lesions may show dermal melanophages

### Cytologic Features

- Tzanck smear may show neutrophils ± eosinophils

## ANCILLARY TESTS

### Immunofluorescence

- Negative for deposits of antibody and complement

## DIFFERENTIAL DIAGNOSIS

### Infections

- e.g., tinea, varicella, scabies, impetigo, congenital syphilis
- Diagnosis is often based on correlation of clinical and pathological findings
- Ancillary studies, such as Gram stain, GMS stain, and cultures of lesions, as well as serological examination and complete blood count assist with final diagnosis

### Acropustulosis of Infancy

- Lesions involve primarily acral skin
- Recurrent breakouts of decreasing frequency and severity may persist for 2-3 years
- Histologic findings overlap with those seen in TNPM

### Erythema Toxicum Neonatorum

- Lesions are surrounded by erythematous wheals
- Histologic examination shows eosinophilic folliculitis and subcorneal eosinophilic pustules

### Eosinophilic Pustular Folliculitis of Infancy

- Commonly involves scalp
- Predominantly affects males
- Cyclic breakouts may occur and are often accompanied by peripheral eosinophilia
- **Vesiculopustules arise on erythematous base**
- Histologic examination shows eosinophilic spongiosis and mixed perifollicular inflammatory infiltrate

### Langerhans Cell Histiocytosis

- Most commonly involves scalp and flexures
- ± systemic involvement
  - Hashimoto-Pritzker disease: Congenital, self-healing variant of Langerhans cell histiocytosis (LCH) without systemic involvement
  - Letterer-Siwe disease: Acute variant of LCH with disseminated involvement
  - Hand-Schüller-Christian disease: Chronic variant of LCH with multifocal systemic involvement
- Histologic examination shows infiltrate of Langerhans cells [CD1a and S100 (+)]

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5. Barr RJ et al: Transient neonatal pustular melanosis. *Int J Dermatol.* 18(8):636-8, 1979



## Acropustulosis of Infancy

## KEY FACTS

## TERMINOLOGY

- Infantile acropustulosis

## CLINICAL ISSUES

- Age of onset
  - Predominantly occurs during first 3 years of life
  - **Not limited to young children**
- Site of involvement
  - Primarily acral skin
- Clinical findings and course
  - Small, pruritic erythematous papules
  - Papules soon evolve to pruritic vesicopustules
  - Healed lesions may show hyperpigmentation and scales
- Prognosis
  - Recurrent breakouts of decreasing frequency and severity may persist for 2-3 years

## MICROSCOPIC

- Subcorneal pustules containing eosinophils (early) &/or neutrophils (late)


## ANCILLARY TESTS

- Negative for deposits of antibody and complement
- CBC may show eosinophilia
- Bacterial and viral cultures of lesions are negative unless associated with secondary infection

## TOP DIFFERENTIAL DIAGNOSES

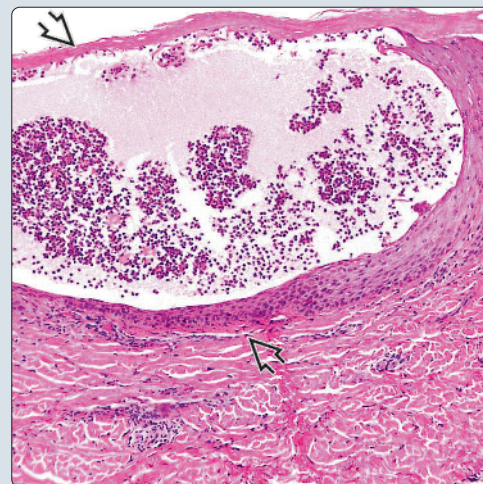
- Erythema toxicum neonatorum
- Transient neonatal pustular melanosis
- Eosinophilic pustular folliculitis of infancy
- Pustular psoriasis
- Infantile scabies
- Viral, bacterial, or fungal infectious dermatoses

## Acral Involvement



(Left) Small vesicles and erythematous papules involve the acral skin of this infant with acropustulosis of infancy (AI). (Courtesy S. Vanderhooft, MD.) (Right) Biopsy specimen of AI shows a subcorneal, intraepidermal pustule with a predominance of eosinophils . (Courtesy M. Chaffins, MD.)

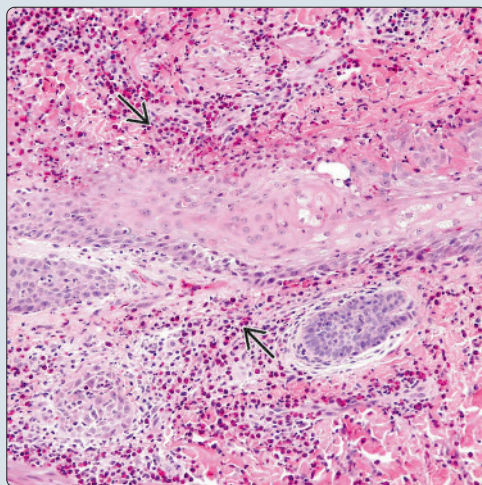


## Intraepidermal Pustule With Eosinophils

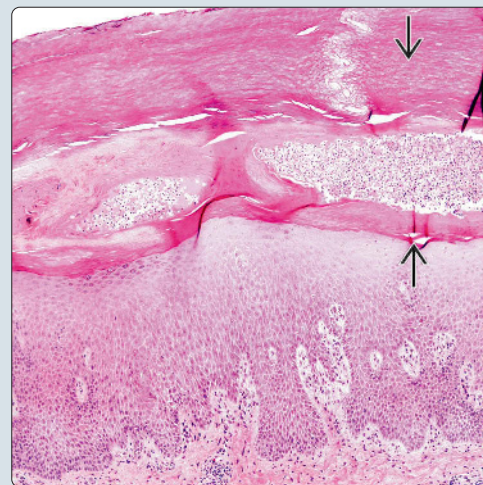


## Erythema Toxicum Neonatorum

(Left) Erythema toxicum neonatorum (ETN) can present as subcorneal pustules filled with eosinophils. Unlike AI, however, ETN shows eosinophilic folliculitis . (Right) H&E shows acral skin involvement by infectious pustular dermatosis. Unlike AI, this intracorneal pustule spares the epidermis .



## Infectious Pustular Dermatitis



## TERMINOLOGY

### Abbreviations

- Acropustulosis of infancy (AI)

### Synonyms

- Infantile acropustulosis

## ETIOLOGY/PATHOGENESIS

### Etiology

- Unknown
- Scabies infestations may precede or be associated with AI

## CLINICAL ISSUES

### Epidemiology

- Age
  - Predominantly occurs during first 3 years of life
  - **Not limited to young children**
  - Rare congenital cases have been reported
- Sex
  - Although initial reports described male predominance, larger series have shown no gender predilection
- Ethnicity
  - Larger series have shown no ethnic predilection

### Site

- Involves primarily acral skin
  - **Palms, soles**, dorsum of hands/feet, wrists, ankles
- Lesions rarely occur in face, scalp, trunk, and buttocks

### Presentation

- Small, pruritic erythematous papules
- Absence of systemic manifestations

### Laboratory Tests

- CBC may show eosinophilia
- Bacterial and viral cultures of lesions are negative unless associated with secondary infection

### Natural History

- Papules soon evolve to pruritic vesicopustules
- Resolution of lesions usually occurs in ~ 2 weeks
- Healed lesions may show hyperpigmentation and scales
- Recurrent breakouts of decreasing frequency and severity may persist for 2-3 years

### Treatment

- Often unnecessary
  - Topical steroids, topical pramoxine, and oral dapsone may be used to improve pruritus

### Prognosis

- Benign, self-limited dermatosis

## MICROSCOPIC

### Histologic Features

- Subcorneal pustules containing eosinophils (early) &/or neutrophils (late)
  - Roof of pustule is composed of compact keratin
  - Base consists of atrophic malpighian layer

- Superficial mixed perivascular inflammatory infiltrate in papillary dermis

### Cytologic Features

- Tzanck smear may show neutrophils ± eosinophils

## ANCILLARY TESTS

### Immunofluorescence

- Negative for deposits of antibody and complement

## DIFFERENTIAL DIAGNOSIS

### Erythema Toxicum Neonatorum

- Usually spares palms and soles
- Lesions are surrounded by erythematous wheals
- Histologic examination shows eosinophilic folliculitis

### Transient Neonatal Pustular Melanosis

- Presents at birth or during 1st 24 hours of life
- Presents as vesicopustules with nonerythematous base
- Lesions do not tend to recur
- Histologic findings overlap with those seen in AI

### Eosinophilic Pustular Folliculitis of Infancy

- Presents as yellow pustules and papules, usually involving scalp
- Histologic examination shows eosinophilic spongiosis and mixed perifollicular inflammatory infiltrate

### Pustular Psoriasis

- Rarely occurs in infants
- Intraepidermal sterile pustule with neutrophils; no eosinophils

### Infantile Scabies

- Diagnostic finding is presence of mite, scybala (feces), or eggs in scrapings from lesions

### Varicella

- History of exposure to infected contact
- Lesions in different healing stages
- Tzanck smear shows multinucleated giant cells and epithelial cells with eosinophilic intranuclear inclusion bodies
- Varicella-zoster virus may be isolated by polymerase chain reaction or culture of lesions

### Hand, Foot, and Mouth Disease

- Systemic prodromic symptoms
- Mucosal involvement
- Caused by coxsackievirus

### Bacterial or Fungal Infectious Dermatoses

- Organisms may be highlighted by stains (Gram, PAS, and GMS) or isolated by culture

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# Pemphigoid Gestationis

## KEY FACTS

### TERMINOLOGY

- Gestational pemphigoid, herpes gestationis
- Autoimmune blistering disease of skin, developing in late pregnancy or early postpartum period

### ETIOLOGY/PATHOGENESIS

- Autoantibodies to NC16A terminus BPAG2
- Can be associated with other autoimmune diseases including Graves disease
- Rarely associated with hydatidiform moles and choriocarcinomas

### CLINICAL ISSUES

- Typically resolves in late pregnancy or spontaneously after delivery
- May persist after delivery and recur in subsequent pregnancies, menstruation, or initiation of oral contraceptive pills
- Increased association with HLA-DR3 and HLA-DR4 alleles

### MACROSCOPIC

- Tense bullae or urticarial lesions with severe pruritus

### MICROSCOPIC

- Subepidermal cleft or bullae with abundant eosinophils
- Eosinophilic spongiosis
- Superficial perivascular infiltrate with lymphocytes, neutrophils, and often eosinophils

### ANCILLARY TESTS

- Direct immunofluorescence shows linear deposition C3  $\pm$  IgG at dermal-epidermal junction
- Salt-split skin and ELISA to distinguish from pruritic urticarial papules and plaques of pregnancy (PUPPP)

### TOP DIFFERENTIAL DIAGNOSES

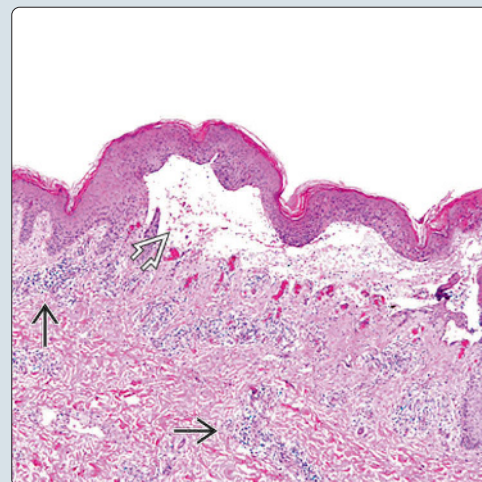
- PUPPP
- Allergic contact dermatitis
- Drug-induced pemphigoid

Urticarial Papules and Plaques

(Left) Clinically, pemphigoid gestationis (PG) presents with urticarial papules and plaques with tense bullae on the abdomen and lower legs. (Courtesy Victor D. Newcomer, MD collection at UCLA and Logical Images, Inc.) (Right) Biopsy of PG demonstrates a typical subepidermal bulla with abundance of eosinophils within the blister cavity as well as a superficial perivascular lymphocytic infiltrate. This is histologically indistinguishable from BP.

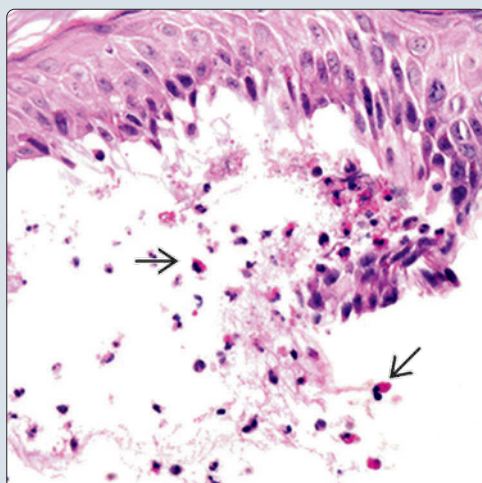


Subepidermal Blister

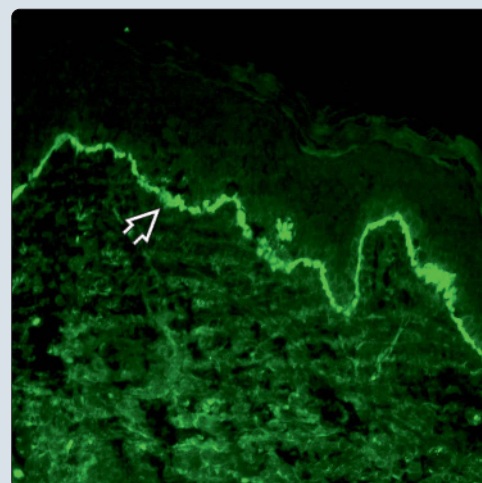


Eosinophilic Infiltrate

(Left) High-power view of PG shows numerous eosinophils admixed with neutrophils and lymphocytes within the subepidermal bulla. (Right) Direct immunofluorescence of PG shows linear deposition of C3 and occasional IgG at the dermal-epidermal junction. (Courtesy K. Leiferman, MD.)



Linear C3 on Immunofluorescence





## TERMINOLOGY

### Abbreviations

- Pemphigoid gestationis (PG)

### Synonyms

- Gestational pemphigoid, herpes gestationis

### Definitions

- Autoimmune blistering disease of skin, developing in late pregnancy or early postpartum period

## ETIOLOGY/PATHOGENESIS

### Autoimmunity

- Antibodies against NC16A terminus of BP antigen 2 (BP180, collagen XVII) at dermal-epidermal junction, along with C3 deposition at basement membrane
- Can be associated with other autoimmune diseases including Graves disease

### Malignancy

- Rarely associated with hydatidiform moles and choriocarcinomas

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - 1 case per 50,000 people per year
  - Increased association with HLA-DR3 and HLA-DR4 alleles

### Presentation

- Pruritic urticarial lesions, tense vesicles, and bullae developing during 2nd or 3rd trimester or early postpartum period; may flare with delivery or just before onset of labor
- Site
  - Typically begins on trunk, often periumbilical, sparing face, palms, and soles

### Natural History

- Typically resolves in late pregnancy or spontaneously after delivery
- May persist after delivery and recur in subsequent pregnancies, menstruation, or initiation of oral contraceptive pills

### Treatment

- Options, risks, complications
  - Placental calcifications and small for gestational age births with systemic corticosteroids
  - May affect up to 10% of newborns but is typically mild presentation
- Adjuvant therapy
  - IVIG for refractory cases
- Drugs
  - Systemic corticosteroids
  - Steroid-sparing agents
    - Oral antihistamines, dapsone, pyridoxine, cyclosporine, methotrexate, gold, azathioprine, sulfapyridine, pyridoxine, cyclophosphamide
  - Topical therapy: Corticosteroids
  - Other: IVIG, plasmapheresis

### Prognosis

- Development of herpes gestationis may increase future risk of Graves disease

## MICROSCOPIC

### Histologic Features

- Bullous lesions
  - Subepidermal cleft or bullae with abundant eosinophils
  - Eosinophilic spongiosis
  - Superficial perivascular infiltrate with lymphocytes, neutrophils, and often eosinophils
- Urticarial lesions
  - Superficial perivascular neutrophilic and lymphocytic infiltrate often with eosinophils
  - Usually indistinguishable from urticarial bullous pemphigoid (BP)

## ANCILLARY TESTS

### Immunofluorescence

- Direct immunofluorescence (DIF) of perilesional skin shows linear deposition C3 in 100% of cases &/or IgG at dermal-epidermal junction (25% of cases)
- Indirect immunofluorescence salt-split skin linear deposition of antibodies at base of epidermal fragment

### Serologic Testing

- ELISA testing for BP180-NC16A can help distinguish this from pruritic urticarial papules and plaques of pregnancy (PUPPP)

## DIFFERENTIAL DIAGNOSIS

### Histological and Clinical Differential Diagnosis

- Drug-induced BP
  - May have identical histology but with history of drug exposure, including diuretics, captopril, D-penicillamine, antibiotics, gold, potassium iodide
- PUPPP
  - Perivascular lymphocytic infiltrate with eosinophils, spongiosis, parakeratosis, and negative DIF
  - Intensely pruritic eruption that typically begins periumbilically in abdominal striae during 3rd trimester
- Allergic contact dermatitis
  - Associated spongiosis with spongiotic vesicles and eosinophils
  - History of exposure and distribution suggestive of exposure

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## KEY FACTS

### TERMINOLOGY

- Bullous eruption of diabetes
- Diabetic bullae
- Bullae

### CLINICAL ISSUES

- Affects men more than woman
- Classically affects distal legs more than arms
- Heals spontaneously

### MICROSCOPIC

- Cell-poor subepidermal bullae in early lesions
- DIF negative

### TOP DIFFERENTIAL DIAGNOSES

- Bullous pemphigoid
  - Tends to be pruritic
  - Due to autoantibodies with prominence of IgG > C3 at dermal-epidermal junction (DEJ)

- Cell-rich subepidermal bullae with eosinophils
- Binds to roof on salt-split skin
- Epidermolysis bullosa acquisita
  - Primarily acral in distribution
  - Type VII collage Ab positive at DEJ
  - Cell-poor, subepidermal bullae
  - Binds to floor on salt-split skin
- Porphyria cutanea tarda
  - Primarily acral or photo in distribution
  - Cell-poor subepidermal bullae
  - DIF shows immunoglobulins and complement surrounding superficial vascular structures

Large Flaccid Bulla

(Left) Large partially collapsed flaccid bulla on the leg of a diabetic patient is seen here. (Courtesy E. Lilly, MD.) (Right) Close-up image showing the retained serous fluid within the flaccid bulla is seen here. (Courtesy E. Lilly, MD.)



Bulla With Retained Serous Fluid

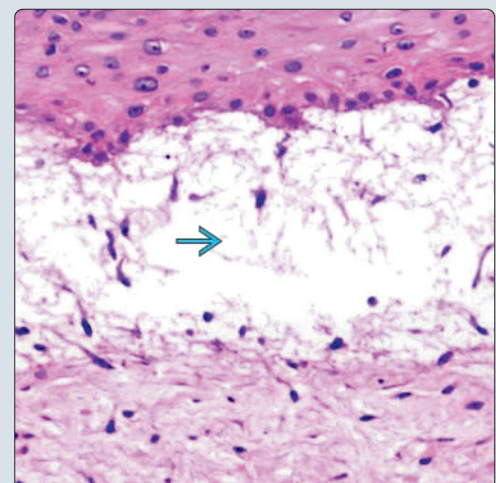


Subepidermal Blister With Stasis Changes

(Left) Cell-poor subepidermal clefting with focal stasis-type changes and edematous stroma is seen here. (Courtesy L. Cohen, MD.) (Right) Close-up image of cell-poor subepidermal clefting which contains sterile proteinaceous fluid is seen here. (Courtesy L. Cohen, MD.)



Cell Poor Subepidermal Cleft



## TERMINOLOGY

### Synonyms

- Bullous eruption of diabetes
- Diabetic bullae
- Bullae

### Definitions

- Often tense bullae of distal extremities (lower > upper), which tend to arise spontaneously in patients with diabetes

## CLINICAL ISSUES

### Epidemiology

- Sex
  - More common in men than women

### Presentation

- Tends to affect people with longstanding diabetes
- Tend to occur spontaneously
- Presents as tense bullae (often several centimeters) on distal extremities
  - Lower extremities more often involved than upper extremities

### Prognosis

- Tends to heal spontaneously unless it becomes secondarily infected

## MICROSCOPIC

### Histologic Features

- Classically presents as cell-poor, subepidermal blister
  - Blister can be intracellular in older lesions
- Within blister, sterile proteinaceous material is typically present
  - Usually contains no or very few inflammatory cells
- Capillary wall thickening or dermal sclerosis may be present in dermis
  - Most likely secondary to patient's chronic, long-standing diabetes
- Caterpillar bodies as seen in porphyria cutanea tarda have been rarely reported in biopsies of bullous diabeticorum

## ANCILLARY TESTS

### Immunofluorescence

- Direct immunofluorescence (DIF) studies are negative
  - Helps distinguish from true immunobullous disorders

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Bullous pemphigoid
  - Often presents with prominent eosinophils
  - DIF shows IgG>C3 prominence of dermal-epidermal junction (DEJ) in n-serrated pattern
  - Binds to roof of salt-split skin
- Epidermolysis bullosa acquisita
  - Cell-poor, subepidermal bullae
  - DIF shows IgG>C3 prominence of DEJ in a u-serrated pattern
  - Binds to floor of salt-split skin

- Type VII collagen Ab positive at DEJ
- Porphyria cutanea tarda
  - Cell-poor, subepidermal bullae
  - DIF shows immunoglobulins and complement surrounding superficial vascular structures

### Clinical

- Bullous pemphigoid
  - Classically on trunk of elderly
  - Very pruritic
  - Classically shows subepidermal blister with numerous eosinophils
    - DIF demonstrates linear IgG &/or C3 along basement membrane zone
- Epidermolysis bullosa acquisita
  - Primarily acral in distribution
- Porphyria cutanea tarda
  - Primarily acral (or photodistribution)
  - History of hepatitis C, alcoholism, or hemochromatosis can cause it
  - Wood lamp can show coral pink fluorescence of urine due to porphyrins

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Lower extremities of long-standing diabetics

### Pathologic Interpretation Pearls

- Cell-poor bullae
- Negative DIF

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## KEY FACTS

### ETIOLOGY/PATHOGENESIS

- Occurs alone, in conjunction with known psoriasis, or as drug reaction to anti-TNF therapy
- Rarely as bacterid reaction or metal allergy
- 95% of patients are active smokers

### CLINICAL ISSUES

- F > M
- Typical age of onset: 40-60 years
- Small sterile pustules on red scaly plaques symmetrically on palms and soles
- May be seen in SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis)

### MICROSCOPIC

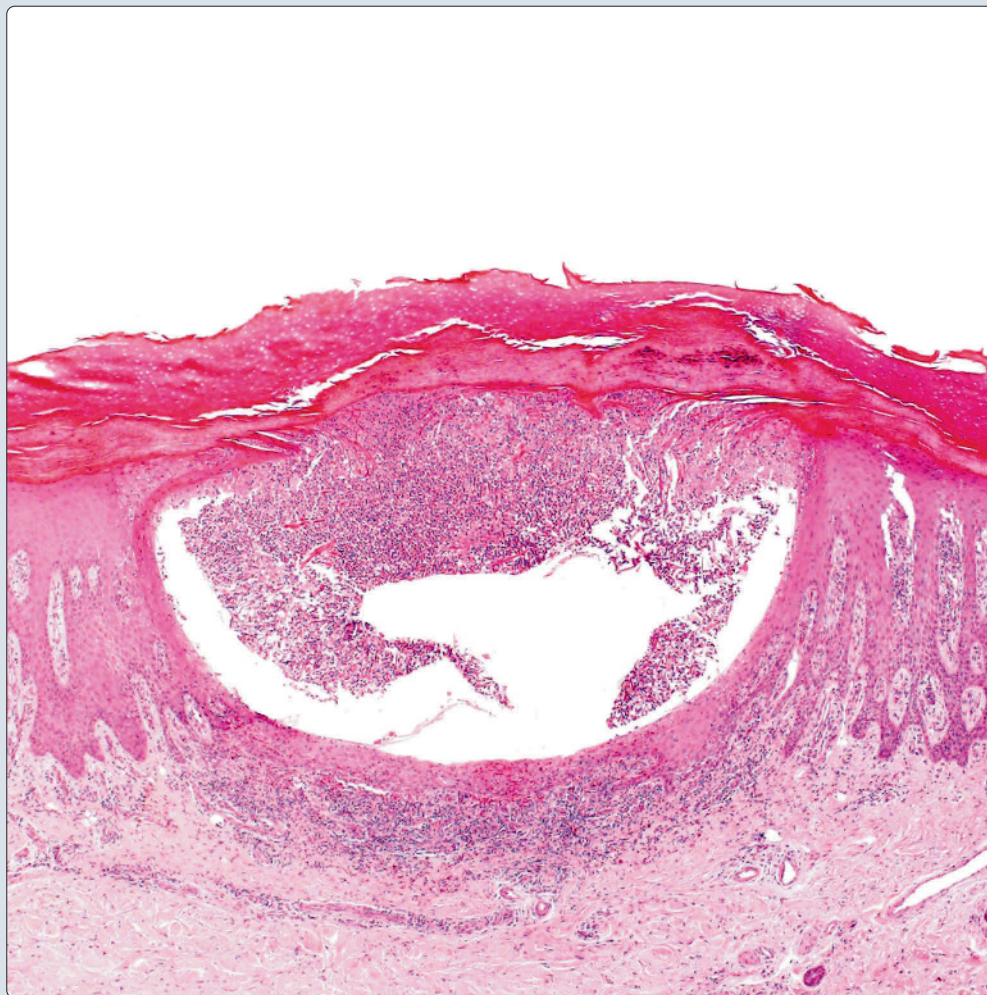
- Intraepidermal spongiotic pustulosis
- Early lesions show lymphocytic exocytosis in superficial dermis
- Neutrophils infiltration present with pustule

- $\pm$  overlying parakeratosis or Munro abscesses
- Dermis with mixed perivascular and diffuse infiltrate of inflammatory cells

### TOP DIFFERENTIAL DIAGNOSES

- Dyshidrotic eczema
  - May be difficult to distinguish histopathologically
- Infection
  - Organism stains may be used to rule out infection although clinical history will usually suffice to exclude this possibility

**Intraepidermal Spongiotic Pustule Filled With Neutrophils**



*Biopsy of palmoplantar pustulosis demonstrates an intraepidermal pustule composed of numerous neutrophils. The main histopathologic differential diagnosis is with dyshidrotic dermatitis.*

## TERMINOLOGY

### Synonyms

- Pustulosis palmaris et plantaris
- Palmoplantar pustular psoriasis
- Pustulosis of palms and soles

## ETIOLOGY/PATHOGENESIS

### Causes

- Occurs alone, in conjunction with known psoriasis, or as drug reaction to anti-TNF therapy
  - Rarely as bacterid reaction or metal allergy
- 95% of patients are active smokers

## CLINICAL ISSUES

### Epidemiology

- Age
  - Typical onset: 40-60 years
- Sex
  - F > M

### Presentation

- Small sterile pustules on red scaly plaques symmetrically on palms and soles
  - May be clinically indistinguishable from dyshidrotic eczema
- Associated findings
  - Sternocostoclavicular ossification in 10% of cases
  - Lytic, sterile bone lesions
  - May be seen in SAPHO syndrome (**s**ynovitis, **a**cne, **p**ustulosis, **h**yperostosis, and **o**steitis)

### Treatment

- Lifestyle
  - Smoking cessation
- Topical therapies
  - Topical corticosteroids
  - PUVA
- Systemic therapies
  - Retinoids
  - Cyclosporine
  - Methotrexate
- Biologics
  - Etanercept
  - Ustekinumab (anti-IL-12/23)
  - Tocilizumab (anti-IL-6)

### Prognosis

- Course is usually chronic

## MICROSCOPIC

### Histologic Features

- Intraepidermal spongiotic pustulosis
- Early lesions show lymphocytic exocytosis in superficial dermis
- Neutrophils infiltration present with pustule
- ± overlying parakeratosis or Munro abscesses
- Dermis with mixed perivascular and diffuse infiltrate of inflammatory cells

## DIFFERENTIAL DIAGNOSIS

### Dyshidrotic Eczema

- May be difficult to distinguish histopathologically

### Infection

- Organism stains may be used to rule out infection although clinical history will usually suffice to exclude this possibility
  - Occasionally organisms will be visible on H&E alone
- Culture may be helpful

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# Erosive Pustular Dermatitis

## KEY FACTS

### TERMINOLOGY

- Synonyms
  - Erosive pustular dermatosis of scalp (EPDS)
  - EPDS and extremities

### ETIOLOGY/PATHOGENESIS

- Has been reported to occur after herpes zoster
- May be preceded by traumatic event of some sort
- May be associated with exposure to certain medications

### CLINICAL ISSUES

- Effective medications for treatment
  - Dapsone, oral prednisone, topical tacrolimus, topical steroid cream
- Clinical course
  - With effective treatment, lesions resolve within 2 weeks to 2 months
  - Complete resolution without recurrence

### MICROSCOPIC

- In biopsies of acute phase, often neutrophil-predominant infiltrate
- With time, inflammatory infiltrate consists of neutrophils, eosinophils, lymphocytes, and plasma cells
- Areas of scarring and alopecia are often seen
- May have secondary colonization by bacteria or fungi-like *Candida*, but true infection does not usually occur

### TOP DIFFERENTIAL DIAGNOSES

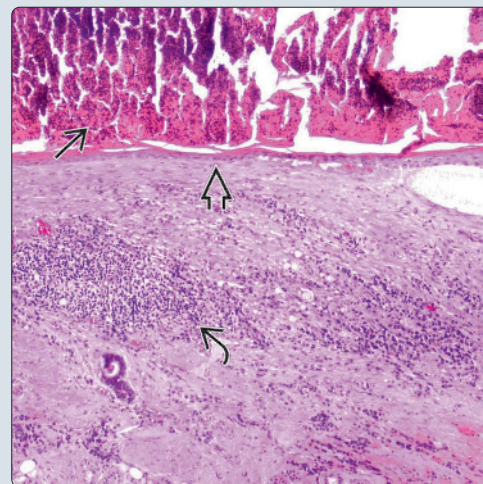
- Pyoderma gangrenosum
- Dissecting cellulitis
- Ulcer with cellulitis
- Tinea capitis or bacterial infection
- Side effect of radiation treatment
- Malignancy

### Erosions and Crusting

(Left) Erosive pustular dermatosis is characterized by prominent skin erosions with overlying purulent scale/crust. (Right) Under the microscope, the areas of crusting [E] are easy to identify and are typically accompanied by areas of erosion &/or pustules. It often occurs on areas of epidermal atrophy [F]. In more chronic cases, the inflammatory infiltrate may be predominantly lymphocytes and plasma cells [G].

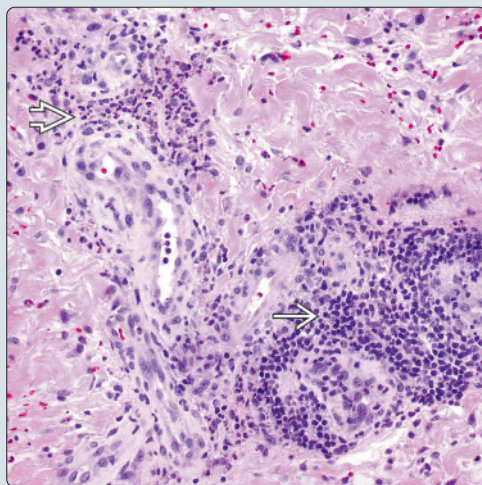


### Epidermal Atrophy With Crust

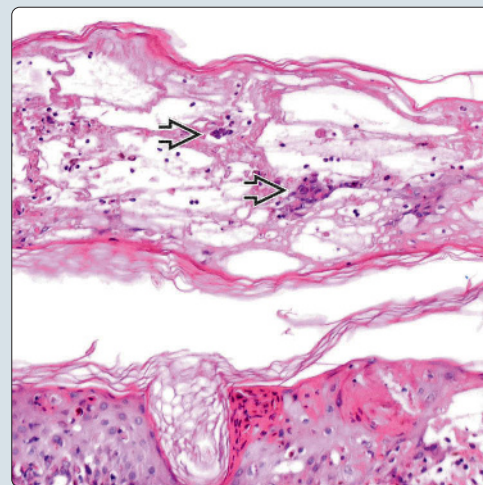


### Mixed Inflammation

(Left) In this example, the inflammatory cell infiltrate has a mixture of neutrophils [E] and lymphocytes [F]. There are also some extravasated red blood cells. (Right) Herpes zoster has been reported to be an antecedent event to erosive pustular dermatosis. Although the background features may appear similar in both diseases, herpes infection has the characteristic nuclear changes of varicella-zoster infection [G].



### Precursors to Erosive Pustular Dermatitis





## TERMINOLOGY

### Synonyms

- Erosive pustular dermatitis of scalp (EPDS)
- EPDS and extremities

### Definitions

- Erosions and pustules with overlying crust, which results in scarring (cicatricial) alopecia
- Often occurs in areas with skin atrophy &/or actinic damage

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- Has been reported to occur after herpes zoster

### Trauma

- CO<sub>2</sub> laser and photodynamic therapy
- Radiation therapy and burns
- Birth trauma
- Liquid nitrogen
- Surgery, skin grafting, and hair transplantation

### Medications

- 5% fluorouracil cream
- Topical latanoprost
- Topical minoxidil
- Others

## CLINICAL ISSUES

### Presentation

- Areas of erosion/ulceration, pustules, and crusting arising in area of alopecia
  - May present as nonhealing wound
- Often history of antecedent trauma or other inciting factor
- With prolonged duration, cicatricial alopecia develops

### Treatment

- Drugs
  - Dapsone
  - Oral prednisone
  - Topical tacrolimus
  - Topical steroid cream

### Prognosis

- With effective treatment, lesions resolve within 2 weeks to 2 months
  - Complete resolution without recurrence

## MICROSCOPIC

### Histologic Features

- In biopsies of acute phase, often neutrophil-predominant infiltrate
- With time, inflammatory infiltrate consists of neutrophils, eosinophils, lymphocytes, and plasma cells
- Areas of scarring and alopecia are often seen
- May have secondary colonization by bacteria or fungi like *Candida*, but true infection does not usually occur
- Epidermis surrounding ulcer often has large, reactive keratinocytes
  - May resemble those seen in actinic keratosis

- No sinus tracts are present

## ANCILLARY TESTS

### Histochemistry

- PAS-positive fungal organisms may be present in crust
  - Tinea capitis or invasive fungal infection are not seen
- Gram staining may identify colonizing bacteria in overlying crust
  - No bacteria should be present in dermis, even in areas resembling abscess

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Pyoderma gangrenosum
  - Diffuse neutrophilic infiltrate with ulceration
  - May be preceded by trauma
  - Not localized to scalp or areas of alopecia
- Dissecting cellulitis
  - Mixed inflammatory cell infiltrate
  - Usually has sinus tracts
  - Clinically will involve larger area of scalp with palpable boggy dermis
  - Not just single area of erosion/ulceration
- Ulcer with cellulitis
  - Ulceration with surrounding dermal neutrophilic infiltrate
  - May be impossible to distinguish without right clinical history and suspicion
- Tinea capitis
  - Fungal hyphae can be seen in hair follicles &/or shafts, confirmed with PAS stain
- Bacterial infection
  - Bacteria should be seen in tissue, not just within overlying crust
  - Gram stain can indicate what type(s) of bacteria may be causative

### Clinical

- Side effect of radiation treatment
  - EPDS has been reported to occur after radiation, so this distinction may be difficult or impossible
  - Atypical stellate fibroblasts should be present in dermis
- Malignancy
  - Invasive tumor should be present underneath or around ulcer
- Diagnoses included in histological differential

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# Porphyria Cutanea Tarda

## KEY FACTS

### ETIOLOGY/PATHOGENESIS

- Caused by deficiency in enzyme uroporphyrinogen decarboxylase

### CLINICAL ISSUES

- Photosensitivity seen in sun-exposed areas (hands, arms, ears, and face)
- Tense nonerythematous vesicles and bullae with erosions and ulcers
- Healing scars, milia formation, and dyspigmentation of affected skin
- Sclerodermoid changes of sun-exposed skin
- Scarring alopecia and onycholysis of nails
- Hypertrichosis of temples and upper and lateral cheeks
- Elevated urinary porphyrins
- Prognosis
  - Chronic episodic flares with excessive exposure to sunlight

### MICROSCOPIC

- Subepidermal blister with cell-poor inflammatory infiltrate
- Festooning of dermal papillae and thick, hyalinized papillary dermal vessels
- Caterpillar bodies at roof of blister
- Perivascular and weak linear basement membrane staining with direct IgG or C3 immunofluorescence

### ANCILLARY TESTS

- IgG or C3 at dermal-epidermal junction (DEJ) and around superficial blood vessels

### TOP DIFFERENTIAL DIAGNOSES

- Pseudoporphyria
- Toxic epidermal necrolysis
- Bullous pemphigoid (cell poor)
- Epidermolysis bullosa acquisita
- Bullous amyloidosis
- Bullous lupus erythematosus

**Blisters and Erosion of Porphyria Cutanea Tarda on Sun-Exposed Areas**

(Left) Blisters and erosions happen frequently on sun-exposed areas (frequently involving the hands and fingers). (Right) Skin manifestations of porphyria are best characterized by blister formation.

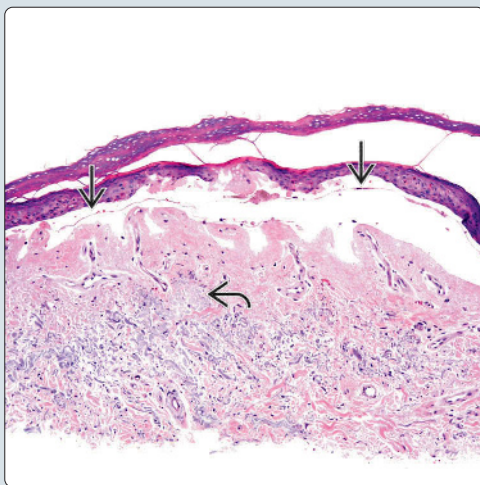


**Blister Formation of Porphyria Cutanea Tarda on Hands**

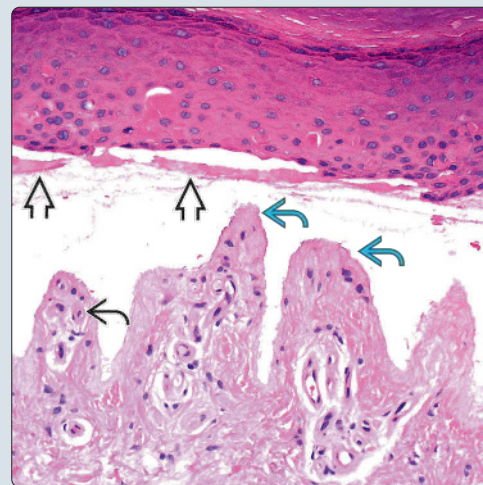


**Subepidermal Cell-Poor Blister With Festooning of Dermal Papillae**

(Left) Histologically, porphyria cutanea tarda (PCT) shows a subepidermal cell-poor blister with festooning of dermal papillae and caterpillar bodies. Prominent solar elastosis is also seen in the dermis. (Right) High-power view of PCT shows festooning of dermal papillae, hyalinized dermal blood vessels, and caterpillar bodies in the roof of the blister. (Courtesy S. Billings, MD.)



**Festooning of Dermal Papillae With Caterpillar Bodies**



## TERMINOLOGY

### Abbreviations

- Porphyria cutanea tarda (PCT)

### Definitions

- Group of heterogeneous metabolic disorders caused by errors in heme synthesis
  - Variants of porphyria besides PCT include
    - Variegate porphyria
    - Hereditary coproporphyria
    - Erythropoietic protoporphyria
    - Acute intermittent porphyria (no skin findings)
    - Congenital erythropoietic porphyria
    - Hepatoerythropoietic porphyria
  - PCT is most common variant; caused by deficiency in enzyme uroporphyrinogen decarboxylase

## ETIOLOGY/PATHOGENESIS

### Developmental Anomaly

- Inherited (autosomal dominant or autosomal recessive)
- Error in heme synthesis causes increased intermediate metabolites
  - Activated by UV light producing reactive oxygen species
  - Causes photosensitivity and subsequent tissue damage (vesicles and bullae)

### Environmental Exposure

- UV light (Soret band 400-410)
- Ethanol, oral contraceptives, hepatitis C, HIV, hemochromatosis, and hepatotoxins (dioxin and hexachlorobenzene)

## CLINICAL ISSUES

### Epidemiology

- Age
  - Childhood (inherited)
  - Adult (acquired)

### Presentation

- Photosensitivity seen in sun-exposed areas (hands, arms, ears, and face)
- Tense nonerythematous vesicles and bullae with erosions and ulcers
- Sclerodermoid changes of sun-exposed skin
- Healing scars, milia formation, and dyspigmentation of affected skin
- Hypertrichosis of temples and upper and lateral cheeks
- Scarring alopecia and onycholysis of nails
- Elevated urinary porphyrins

### Laboratory Tests

- Metabolic study for urinary porphyrins, specifically uroporphyrin (300-1,000 µg)
- Pink or coral-red fluorescence of random urine sample
  - With exposure to air or Wood light

### Treatment

- Drugs
  - Hydroxychloroquine or chloroquine
- Patient driven

- Vigilant sun protection
  - Sunblock, long clothing
- Eliminate alcohol, estrogen, and iron ingestion
- Other
  - Common first-line therapy is phlebotomy

### Prognosis

- Chronic episodic flares with excessive exposure to sunlight

## MICROSCOPIC

### Histologic Features

- Paucicellular noninflammatory subepidermal bullae
  - Split at lamina lucida
- Hyalinized, thick papillary dermal vessels
- Festooning of dermal papillae
- Caterpillar bodies
  - Eosinophilic wavy structures (type IV collagen) at roof of blister
- Erythrocytes inside blister
- Dermal sclerosis and prominent solar elastosis

## ANCILLARY TESTS

### Immunofluorescence

- Direct: Nonspecific pattern of IgG or C3 at dermal-epidermal junction (DEJ) and around superficial blood vessels

## DIFFERENTIAL DIAGNOSIS

### Pseudoporphyria

- Occurs with chronic renal failure (dialysis) and medications (tetracycline, NSAIDs, cephalosporins)
- Urinary porphyrin levels are normal

### Toxic Epidermal Necrolysis

- Blister with roof of necrotic epidermis

### Bullous Pemphigoid (Cell Poor)

- If taken from vesicle without erythematous base
- Eosinophils and neutrophils in dermis

### Epidermolysis Bullosa Acquisita

- Noninflammatory subepidermal bullae after skin trauma or sun exposure
- May involve mucous membranes
- Linear IgG and complement along dermal-epidermal junction
- Autoantibodies to type VII collagen

### Bullous Amyloidosis

- Bullae above dermal amyloid deposits

### Bullous Lupus Erythematosus

- Subepidermal bullae with papillary dermal microabscesses
- Neutrophils in papillary dermis and around vessels
- IgG, C3, and IgA along DEJ

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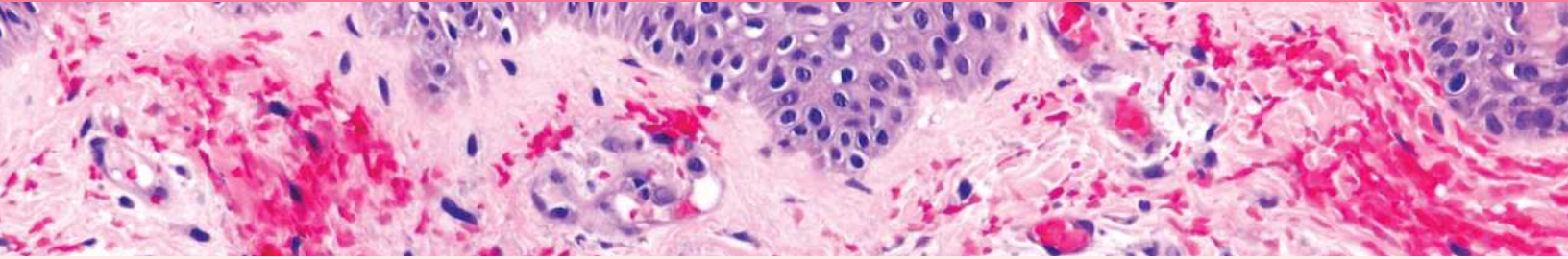
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## SECTION 4

# Vasculitis, Vasculopathy, and Perivascular Dermatoses



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## KEY FACTS

### TERMINOLOGY

- Not true disease entity but rather histologic reaction pattern seen in variety of diseases

### ETIOLOGY/PATHOGENESIS

- ~ 40% of cases are idiopathic

### CLINICAL ISSUES

- Nonblanching erythematous macules (palpable purpura) with predilection for lower legs
- Timing of biopsy is crucial since older lesions can lose characteristic histology or immunoglobulin deposition

### MICROSCOPIC

- Hallmark histologic features
  - Fibrinoid necrosis of blood vessel walls
  - Endothelial cell swelling
  - Perivascular neutrophilic infiltrate with occasional lymphocytes, eosinophils, or histiocytes (vasculitis)
  - Karyorrhexis (leukocytoclasia) of WBCs

- RBC extravasation

### ANCILLARY TESTS

- Direct immunofluorescence can be helpful but findings depend on age of lesion

### TOP DIFFERENTIAL DIAGNOSES

- Sweet syndrome
- Bowel-associated dermatosis-arthritis syndrome
- Livedo vasculopathy (atrophie blanche)
- Granuloma faciale
- Erythema elevatum diutinum

Palpable Nonblanching Purpura

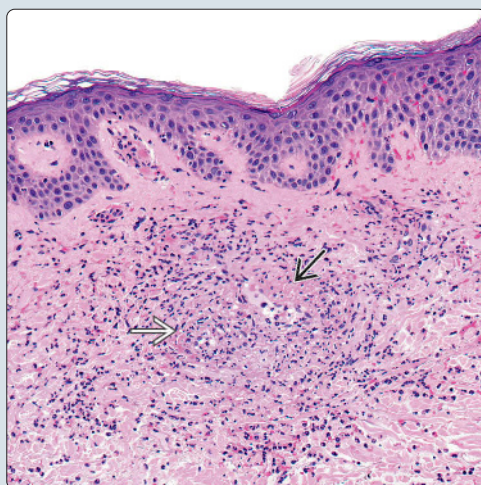


Often Symmetric Lower Extremities Involvement

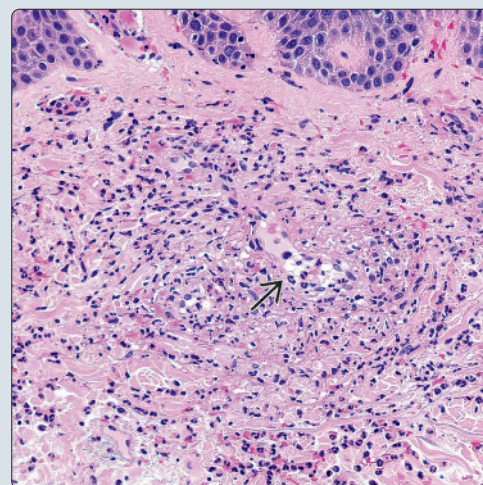


(Left) This is an example of leukocytic vasculitis (LCV) clinically with varying darkness of erythema and petechial lesions on the extremity of a patient who also had bowel ischemia. (Courtesy PMPH-USA Publishing.) (Right) This patient with Henoch-Schönlein purpura (HSP) demonstrates symmetric petechial erythematous papules over the dorsal feet. The patient also had abdominal pain.

Superficial Vascular Plexus Inflammation



Vessel Wall Necrosis



(Left) Low-power view of leukocytoclastic vasculitis demonstrates vessel wall damage, fibrinoid necrosis, and necroinflammatory debris involving a superficial vessel. (Courtesy UCSF Dermatopathology Service.) (Right) Higher power view shows vessel wall necrosis and a prominent polymorphic inflammatory infiltrate composed of eosinophils, neutrophils, and lymphocytes. (Courtesy UCSF Dermatopathology Service.)



## TERMINOLOGY

### Abbreviations

- Leukocytoclastic vasculitis (LCV)

### Synonyms

- Cutaneous small vessel vasculitis, hypersensitivity vasculitis, neutrophilic vasculitis, allergic vasculitis, leukocytoclastic angiitis, necrotizing vasculitis (not preferred terminology)

### Definitions

- Often idiopathic, prototypic, and most common form of vasculitis classically with palpable purpura (hallmark of disease) on legs
  - Not true disease entity but rather histologic vascular reaction pattern secondary to variety of underlying disease states

## ETIOLOGY/PATHOGENESIS

### Pathogenesis

- Due to deposition of immune complexes in blood vessel walls
  - Leads to complement activation and production of C5a
    - Leads to vessel wall injury, fibrin deposition, and release of erythrocytes into perivenular connective tissue (purpura)
- Thromboses may also eventually occur
  - May be due to activation of tumor necrosis factor and interleukin-1 activity

### Etiology

- ~ 40% of cases are idiopathic
- Multiple etiologic groups
  - Infections, drugs, chemicals, foreign proteins, underlying systemic disorders, cancer (rarely)
    - Streptococcal infection, collagen vascular disease, inflammatory bowel disease as well as numerous drugs are most commonly implicated

## CLINICAL ISSUES

### Site

- Predominately lower legs
  - However, can affect variety of sites including arms, feet, ankles, trunk, buttocks, and face

### Presentation

- Nonblanching erythematous macules (palpable purpura) with predilection for lower legs
- Lesions may also be erythema multiforme-like (bull's-eye-like annular erythema), papulonodular, vesicular, bullous, pustular, or ulcerated as well
- Pruritus, fever, malaise, arthralgia, and myalgia may also occur

### Laboratory Tests

- Often beneficial to identify underlying disorder
- Complete blood count, urinalysis, strep throat culture, antistreptolysin titer, hepatitis serologies, &/or antinuclear antibody screen (positive in ~ 20% of cases), cryoglobulins (found in ~ 25% of cases), serum complement, or serum protein electrophoresis may be beneficial

### Prognosis

- Condition is usually self-limited but may recur or become chronic
  - Lesions typically resolve in 3-4 weeks with residual hyperpigmentation
- Estimated that ~ 2% of patients will die of systemic disease
  - Death is usually secondary to renal involvement

### Biopsy

- Timing of biopsy is crucial since older lesions can lose characteristic histology or immunoglobulin deposition

## MICROSCOPIC

### Histologic Features

- Features similar irrespective of underlying disorder
- Hallmark features
  - Fibrinoid necrosis of blood vessel walls
  - Endothelial cell swelling
  - Perivascular neutrophilic infiltrate with occasional lymphocytes, eosinophils, or histiocytes (vasculitis)
  - Conspicuous nuclear dust secondary to karyorrhexis or leukocytoclasia (destructive fragmentation of nucleus of dying neutrophil)
  - RBC extravasation
- LCV is dynamic process, so not all features will be present in all disease stages
- Postcapillary venules and capillary loops (not arterioles) are most often affected
- May have thrombus formation
- May have ischemic necrosis, vesicle, or pustular formation in overlying epidermis

### Variants and Subtypes

- **Henoch-Schönlein purpura**
  - May be histologically indistinguishable from LCV of other causes
  - Direct immunofluorescence (DIF) demonstrates IgA (and sometimes also C3) in vessel walls in involved and uninvolved skin
    - Some cases (especially older necrotic lesions) may be negative by DIF (may represent sampling error)
    - Not pathognomonic for Henoch-Schönlein purpura (HSP) as cryoglobulinemia, drug-induced hypersensitivity vasculitis, and others can also have IgA deposition in vessel walls by DIF
  - Clinically, lesions are typically located on lower legs and accompanied by
    - Arthritis, abdominal pain, hematuria, and occasionally cardiac or neurologic symptoms
- **Urticarial vasculitis**
  - Defined by clinical urticaria with LCV on biopsy
  - Lesions often last 24-72 hours (vs. usual chronic urticaria) and are often painful, burning, or pruritic
  - Often heralds onset of another systemic disease, especially autoimmune disorders
  - Often associated with hypocomplementemia (more often in patients with underlying autoimmune disorder)
  - Often shows leukocytoclasia, extravasated RBCs, and dermal edema
  - Changes can be subtle and clinicopathologic correlation is important

- However, histologic changes can range from subtle vascular injury to full blown necrotizing vasculitis
- **Infectious or septic vasculitis**
  - Can be seen clinically with septicemic states involving following entities
    - *Meningococcus*, *Gonococcus*, *Streptococcus*, *Staphylococcus* (infective endocarditis), some rickettsial infections, and secondary syphilis
  - Cutaneous lesions especially common in meningococcal septicemia (80% or more of cases)
  - Predilection for extremities and pressure sites
  - Findings can be variable depending on infective organism and extent of clinical disease
    - However, small vessel vasculitis is typically present
  - Clinical history especially important in suspected cases
  - Gram stain or other special stains are recommended in any suspected case
- **Eosinophilic vasculitis**
  - Newer, rare entity characterized by
    - Necrotizing eosinophil-rich small vessel vasculitis involving superficial and sometimes deep vessels
    - Can be idiopathic, associated with connective tissue disorders or hypereosinophilic syndrome
- **Cryoglobulinemic vasculitis**
  - Evidence of vasculitis on biopsy with eosinophilic "hyaline" thrombi within vascular lumina that stains positive with periodic acid-Schiff
- Chronic localized form of LCV
- Polymorphous inflammatory infiltrate
- Early lesions may be difficult to distinguish from LCV
  - LCV typically has more neutrophilic nuclear dust, more extravasated erythrocytes, and less dense inflammatory infiltrate
- Erythema elevatum diutinum (EED)
  - Early lesions of EED indistinguishable from LCV
  - Late lesions show
    - "Onion skinning" fibrosis around vessels
    - Extracellular cholesterol clefts

## Clinical (Palpable Purpura)

- HSP
  - Classically, can present as triad of purpura, arthritis, and abdominal pain
- Disseminated gonococcal infection
  - Can present as purpura with fevers and arthralgias
- Rocky Mountain spotted fever
  - After tick bite, it can present as fever, nausea, vomiting, headache, and muscle pain early on; later, can present as centripetally spreading rash, sometimes with petechia, as well as abdominal and joint pain
- Polyarteritis nodosa
  - Life-threatening (via renal failure, myocardial infarction, stroke) disease, which can present as fever, fatigue, weakness, and rash; rash can appear as livedo or purpura at times
- Microscopic polyangiitis
  - Can present as fever, weight loss, fatigue and renal failure; rash can appear as livedo or purpura at times

## ANCILLARY TESTS

### Immunofluorescence

- DIF can be helpful but findings depend on age of lesion
  - Early lesions often show fibrinogen, C3, and IgM
  - Fully developed lesions are often positive for fibrinogen, albumin, and IgG
  - Late lesions demonstrate fibrinogen with some C3

## DIFFERENTIAL DIAGNOSIS

### Histopathologic (Leukocytoclasia)

- Sweet syndrome
  - Early lesions of LCV that lack vascular damage may be difficult to distinguish from Sweet
  - Diffuse vs. perivascular neutrophilic infiltrate
  - Absence of fibrinoid vascular change or necrosis
- Bowel-associated dermatosis-arthritis syndrome
  - Commonly seen with bypass surgery for morbid obesity
  - May be histologically indistinguishable from Sweet syndrome
  - Subepidermal edema; heavy, diffuse, and perivascular neutrophilic infiltrate in upper and mid dermis; and variable leukocytoclasia
  - Fibrin within vessels may be present
- Livedo vasculopathy (atrophie blanche)
  - Can have wedge-shaped epidermal and dermal necrosis
  - Inflammatory infiltrate typically sparse and no vessel wall destruction
  - Fibrinoid material occluding hyalinized blood vessels in upper and mid dermis
- Granuloma faciale
  - Grenz zone

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- LCV may coexist with large vessel vasculitis

## REPORTING

### Key Elements to Report

- Important to comment on presence or absence of larger vessels in biopsy specimen
  - Especially if clinically trying to rule out large vessel vasculitis
- Should be noted whether deep reticular dermis or subcutaneous tissue is present in biopsy specimen

## SELECTED REFERENCES

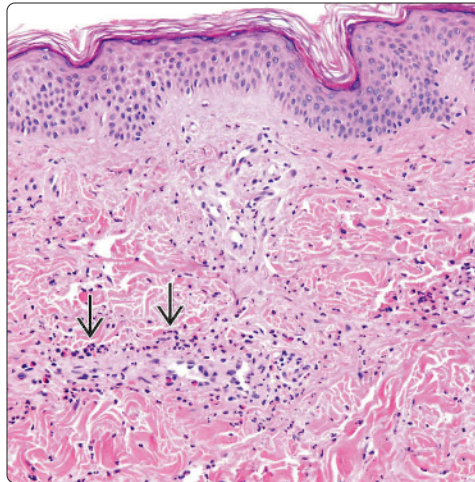
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**Urticarial Plaques (Present > 24 Hours)**

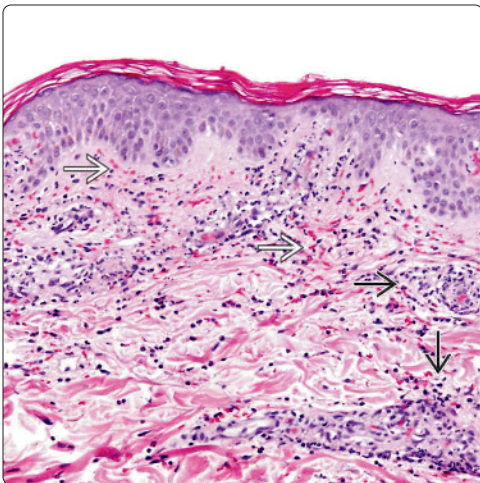


**Mild Perivascular Inflammation**

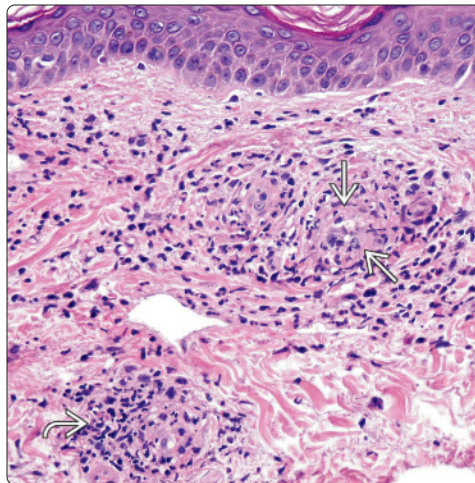


**(Left)** This is urticarial vasculitis over the back of a patient showing oval pink plaques [ ] mimicking urticaria. The inner edge of the lower plaque is beginning to leave behind some characteristic bruising. The plaques were painful and not evanescent. **(Right)** In this example of urticarial vasculitis, the perivascular inflammatory infiltrate [ ] is much milder than in the other examples of LCV or HSP. (Courtesy A. Bowen, MD.)

**Red Blood Cell Extravasation**

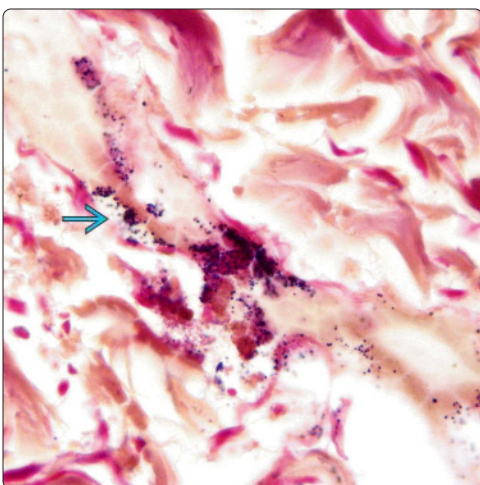


**Henoch-Schönlein Purpura Vasculitis**

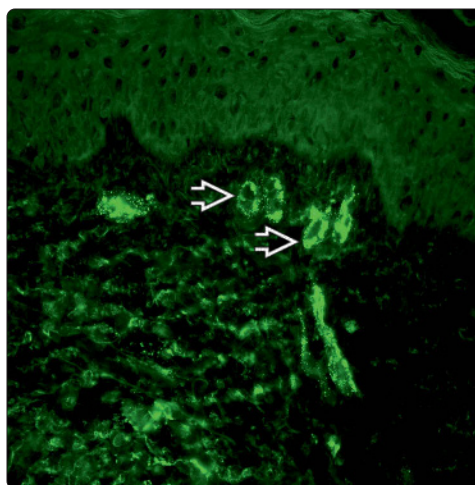


**(Left)** This is a biopsy from a patient with septic vasculitis. Note the perivascular inflammation [ ] and RBC extravasation [ ], indistinguishable from other types of LCV on H&E. Special stains would be indicated. **(Right)** This is an example of HSP. Note that the vessel in the lower left corner is being destroyed by the inflammatory cells [ ]. The fragmentation of the nuclear debris surrounds this vessel (karyorrhexis). In the upper right vessel, note fibrin replacing the lumen [ ]. (Courtesy S. Florell, MD.)

**Iron Stain**



**IgA(+) in Henoch-Schönlein Purpura**



**(Left)** Stain shows Iron remnants [ ] after extravasated RBC are broken down. **(Right)** This is a direct immunofluorescence (DIF) from a patient with HSP showing typical granular staining for IgA in the upper dermal blood vessels [ ]. DIF findings in IgA vasculitis would be indistinguishable. (Courtesy K. Leiferman, MD.)



# Granuloma Faciale

## KEY FACTS

### TERMINOLOGY

- Small vessel leukocytoclastic vasculitis

### CLINICAL ISSUES

- Most commonly occurs in adults but may rarely occur in childhood
- Male patients more frequently affected
- Most commonly presents as red-brown plaques or nodules on face
  - Extrafacial lesions may occur
- Usually solitary lesion, but multiple lesions occur in ~ 1/3 of patients
- Lesions typically very resistant to treatment



### MICROSCOPIC

- Name is misnomer (granuloma referring to clinical appearance of granules) as granulomas are not seen histologically

- Most consistent histologic findings include polymorphous inflammatory infiltrate in upper 2/3 of epidermis
- Grenz zone between inflammatory cell infiltrate and epidermis
- Superficial dermal telangiectasias
- Early lesions may show perivascular neutrophilic infiltrates, leukocytoclasia, and leukocytoclastic vasculitis with fibrin in vessel walls
- Patterned concentric fibrosis surrounding dermal capillaries is often present in later lesions

### TOP DIFFERENTIAL DIAGNOSES

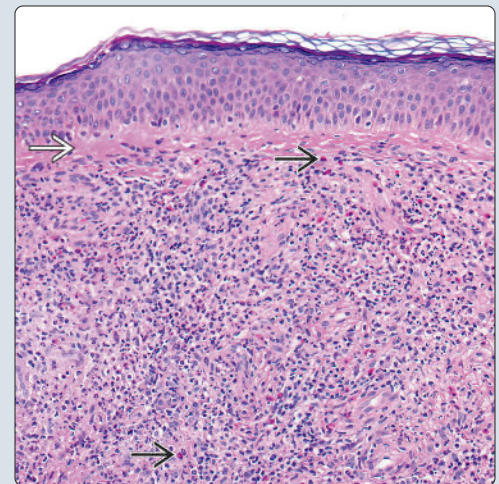
- Sweet syndrome
- Erythema elevatum diutinum
- Localized chronic fibrosing vasculitis
- Leukocytoclastic vasculitis
- Arthropod bite reaction
- Kimura disease/angiolymphoid hyperplasia with eosinophilia





**(Left)** *Granuloma faciale (GF)* can present as reddish-brown, slightly indurated, asymptomatic plaques over the cheeks. This condition most commonly affects Caucasian men. **(Right)** Low-power view of GF shows a dense polymorphous dermal inflammatory infiltrate and evidence of a grenz zone . Note the numerous eosinophils . (Courtesy UCSF Dermatopathology Service.)

Plaques of Granuloma Faciale on Cheeks

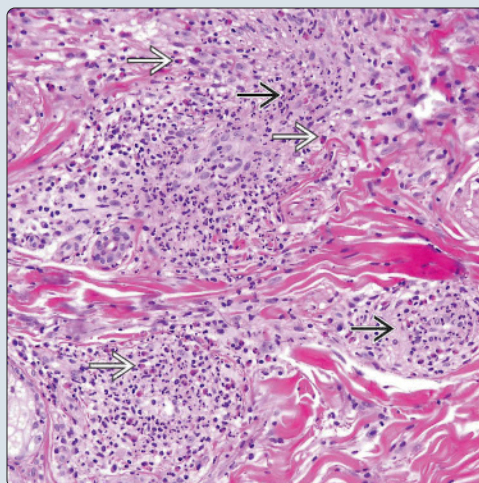


Grenz Zone

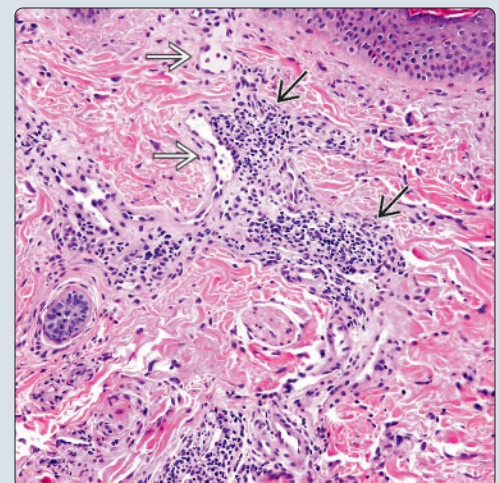


**(Left)** Early GF shows leukocytoclastic vasculitis (LCV)  with a predominantly neutrophilic infiltrate and many eosinophils  as well. **(Right)** GF lesions sometimes show a less dense perivascular neutrophilic inflammatory infiltrate . Note the multiple telangiectasias .

Leukocytoclastic Vasculitis



Mild Inflammation and Telangiectasias



## TERMINOLOGY

### Abbreviations

- Granuloma faciale (GF)

### Definitions

- Small vessel leukocytoclastic vasculitis typically on face with polymorphous inflammatory cell infiltrate

## ETIOLOGY/PATHOGENESIS

### Unknown

- Vascular injury thought to be involved

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Uncommon
- Age
  - Most commonly occurs in adults but may rarely occur in childhood
- Sex
  - Most commonly affects men
- Ethnicity
  - Caucasians are more commonly affected

### Presentation

- Presents as red-brown plaques or nodules on face
  - Extrafacial lesions may also occur
- Usually solitary lesion, but multiple lesions occur in ~ 1/3 of patients

### Treatment

- Lesions typically very resistant to treatment
- Multiple therapies have been used with varying success

### Prognosis

- Excellent as condition is only nuisance for cosmetic reasons

## MICROSCOPIC

### Histologic Features

- Name (GF) is misnomer (granuloma referring to clinical appearance of granules) as granulomas are not seen histologically
- Most consistent histologic findings include polymorphous inflammatory infiltrate in upper 2/3 of epidermis, grenz zone, and telangiectasias
- Polymorphous infiltrate often contains neutrophils (often predominant cell), lymphocytes, plasma cells, and eosinophils
  - Numerous eosinophils often stated to be specific for disease, but 1 large case series showed presence in only 1/2 of cases and were often not prominent
- Extravasated RBCs and hemosiderin are also often present (gives red-brown clinical appearance)
- Early lesions may show perivascular neutrophilic infiltrates, leukocytoclasia, and leukocytoclastic vasculitis (LCV) with fibrin in vessel walls
- PAS(+); diastase resistant eosinophilic fibrinoid material (toxic hyaline) may be deposited around vessels in some lesions

- Patterned concentric fibrosis surrounding dermal capillaries is often present in later lesions

## DIFFERENTIAL DIAGNOSIS

### Sweet Syndrome

- Vasculitis is typically not seen
- Inflammatory infiltrate is monomorphic and contains almost all neutrophils
- Clinically has abrupt onset of tender and painful erythematous plaques in association with fever and malaise
  - Often affects extremities in addition to face

### Erythema Elevatum Diutinum

- Regarded by some to be variant of GF
- Face is usually spared
- Usually targets dorsal aspects of joints and typically affects young women
- Eruption often bilateral and symmetric
- Eosinophils are scant to absent
- Characteristic histology (older lesions) with long parallel arrays of fibrosis dotted with neutrophilic infiltrates

### Localized Chronic Fibrosing Vasculitis

- Proposed to be part of same spectrum of disease as erythema elevatum diutinum (EED) and GF
- Patterned fibrosis and inflammation histologically similar to both EED and GF
  - Distinct on clinical grounds (not affecting extensor extremities symmetrically near joints or face)

### Leukocytoclastic Vasculitis

- Early lesions of GF can look very similar to LCV
- However, LCV typically has more neutrophilic nuclear dust, more extravasated erythrocytes, and less dense inflammatory infiltrate

### Arthropod Bite Reaction

- Polymorphous inflammatory infiltrate is predominantly perivascular and often creates wedge shape
- May see arthropod (tick) parts
- Often tract of necrosis on either side of bite
- Clinically pruritic

### Kimura Disease/Angiolymphoid Hyperplasia With Eosinophilia

- Much rarer than GF (most cases reported in Southeast Asia)
- Epithelioid endothelial cells are hallmark of disease
- Thickened dermal vessels rather than telangiectasia

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## KEY FACTS

### TERMINOLOGY

- Rare form of chronic leukocytoclastic vasculitis (LCV) characterized by repair and fibrosis

### CLINICAL ISSUES

- Persistent nodular, symmetrical eruption, typically on extensor surfaces of extremities
- Lesions can be papules, plaques, or nodules that are red, violaceous, brown, or yellow in color
- Dapsone is drug of choice, and lesions characteristically respond

### MICROSCOPIC

- LCV-like picture in early lesions with predominance of neutrophils
- Older lesions show
  - Capillary proliferation (granulation tissue) with neutrophilic infiltrate
  - Extracellular cholesterol cleft deposits

- Onion-skinning fibrosis surrounding vessels

### TOP DIFFERENTIAL DIAGNOSES

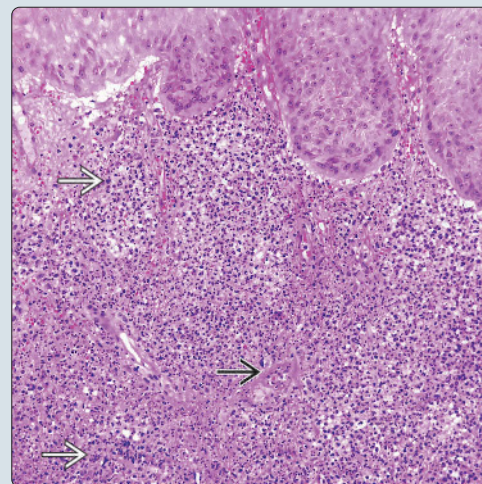
- Granuloma faciale
  - Usually facial location (EED is typically nonfacial and usually acral)
- LCV of other causes
  - Early lesions of EED indistinguishable from LCV
- Chronic fibrosing vasculitis
  - Has been proposed to be part of same spectrum of disease as EED and granuloma faciale
- Sweet syndrome
  - Clinically red, hot tender lesions with fever and neutrophilia
- Behçet disease
  - Diagnosis is primarily clinical
- Rheumatoid neutrophilic dermatosis
  - Very rare cutaneous manifestation of severe rheumatoid arthritis

### Indurated Plaques

(Left) *Erythema elevatum diutinum* (EED) can present as dull red, asymptomatic, chronic, indurated plaques over the knee (extensor surface). (Right) Early EED shows numerous neutrophils within the dermis, indistinguishable from other neutrophilic dermatoses. Note vessel damage just as in leukocytoclastic vasculitis.

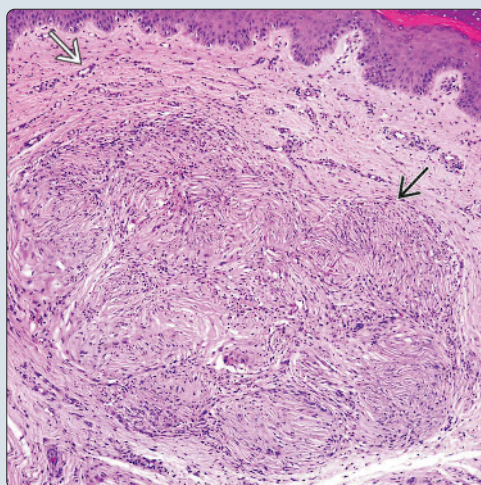


### Diffuse Dermal Neutrophils

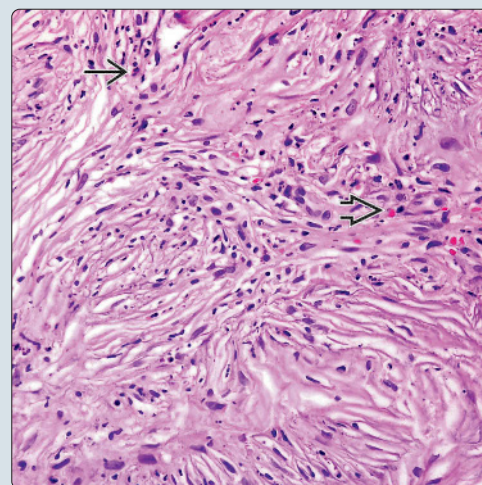


### Nodular Dermal Fibrosis

(Left) Low-power view of late EED demonstrates classic dermal nodular fibrosis surrounded by a capillary proliferation. (Right) Higher power view of late EED demonstrates a storiform pattern of fibrosis with numerous neutrophils and rare extravasated red blood cells.



### Storiform Fibrosis, Neutrophils, and Extravasated Red Blood Cells





## TERMINOLOGY

### Abbreviations

- Erythema elevatum diutinum (EED)

### Definitions

- Rare form of chronic leukocytoclastic vasculitis (LCV) characterized by repair and fibrosis

## ETIOLOGY/PATHOGENESIS

### Unknown

- Proposed to be immune complex mediated
  - Viral or bacterial antigens, especially streptococcal antigen and *Escherichia coli*, have been implicated
  - HIV has been associated with some cases

### Disease Associations

- Paraproteinemia, myelodysplastic syndrome, malignancy (especially hematopoietic), inflammatory bowel disease, celiac disease, and rheumatoid arthritis have all been reported in association with EED

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Very rare disease
  - Largest case series in literature only involved 13 patients
- Age
  - Middle age
- Sex
  - More common in elderly men and young women with rheumatoid disorders

### Presentation

- Persistent nodular, symmetrical eruption, typically on extensor surfaces of extremities
- Lesions can be papules, plaques, or nodules that are red, violaceous, brown, or yellow in color

### Treatment

- Drugs
  - Dapsone is drug of choice, and lesions characteristically respond

### Prognosis

- Generally excellent

## MICROSCOPIC

### Histologic Features

- LCV-like picture in early lesions with predominance of neutrophils
  - Early lesions often indistinguishable from other neutrophilic dermatoses
- Characteristic histologic features in older lesions that include
  - Capillary proliferation (granulation tissue) with neutrophilic infiltrate that can involve almost entire dermis
    - Capillaries may show fibrous thickening or fibrinoid material in lumen, as in early lesions
  - Extracellular cholesterol cleft deposits

- Thought to be secondary to erythrocyte extravasation
- Onion-skinning fibrosis surrounding vessels
  - Entire lesion can become markedly fibrotic and resemble dermatofibroma (DF)
  - Presence of LCV and neutrophilic infiltrate differentiates from DF
  - Scarring can show storiform pattern
  - Foci of neutrophils often found in even most fibrotic specimens
- Older, burnt-out lesions may lack vasculitis

## DIFFERENTIAL DIAGNOSIS

### Granuloma Faciale

- Usually facial location (EED is typically nonfacial and usually acral)
- Typically less fibrosis
- Typically more eosinophils
- Grenz zone present (typically absent in EED)

### Leukocytoclastic Vasculitis of Other Causes

- Early lesions of EED indistinguishable from LCV
- LCV does not share characteristic histologic features of older EED lesions
  - No onion-skinning fibrosis
  - Less fibrosis
  - No cholesterol cleft deposits

### Chronic Fibrosing Vasculitis

- Has been proposed to be part of same spectrum of disease as EED and GF
- Patterned fibrosis and inflammation histologically similar to both EED and GF
- Diagnosis made when clinical features do not match GF or EED

### Sweet Syndrome

- Clinically red, hot tender lesions with fever and neutrophilia
- Early lesions of EED often indistinguishable
- Predominantly neutrophilic infiltrate
- No vasculitis

### Behçet Disease

- Clinical correlation very important because histologic findings are often nonspecific and quite variable
  - Diagnosis is primarily clinical
- Clinically almost always involves 2 of following mucous membranes
  - Eye, mouth, or genital area
  - Biopsy will most often be from 1 of these mucosal sites

### Rheumatoid Neutrophilic Dermatoses

- Very rare cutaneous manifestation of severe rheumatoid arthritis
- Early lesions of EED often indistinguishable

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## KEY FACTS

### TERMINOLOGY

- Vascular reaction of skin consisting of wheals (white or red evanescent plaques) surrounded by red halo or flare and severe itching or stinging lasting 1 to several hours
- Can be classified into acute (symptoms lasting over period of < 6 weeks) and chronic (symptoms lasting over period of > 6 weeks)

### CLINICAL ISSUES

- Extremely common entity occurring in ~ 20% of population at some point during their lifetime
- Presents as transient onset of erythematous or white plaques (wheals) with surrounding red halo (flare) that is often pruritic and edematous

### MICROSCOPIC

- Findings are many times nonspecific and can be quite unimpressive
- Most common findings (when present) include

- Perivascular and interstitial dermal inflammatory infiltrate composed of eosinophils, neutrophils, and lymphocytes
  - Early lesions demonstrate sparser infiltrate typically grouped solely around blood vessels
  - As lesions age, inflammatory cells extend into interstitium and with them edema and vascular dilatation ensue
- Dermal edema (may vary from mild to severe)
- Dilated blood vessels and lymphatic spaces

### TOP DIFFERENTIAL DIAGNOSES

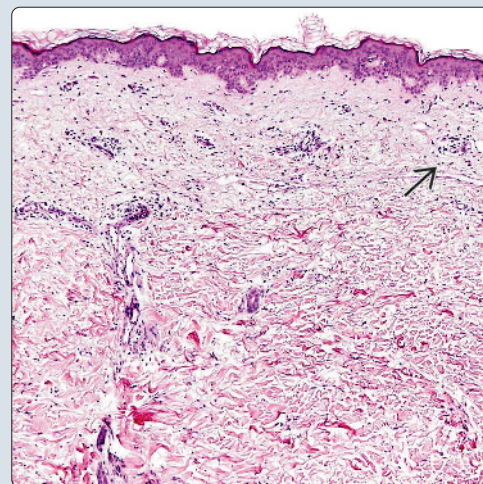
- Arthropod bite
- Urticarial vasculitis
- Dermatophytosis
- Other "invisible" dermatoses

**Pink Papules and Plaques of Chronic Urticaria**

**(Left)** Chronic urticaria shows pink well-demarcated papules and plaques on the forearm. These are very pruritic and evanescent; they will disappear and move to new areas every 24 hours or less. **(Right)** Histologic findings in urticaria can be nonspecific with a sparse polymorphous perivascular infiltrate and interstitial infiltrate with slight dermal edema.

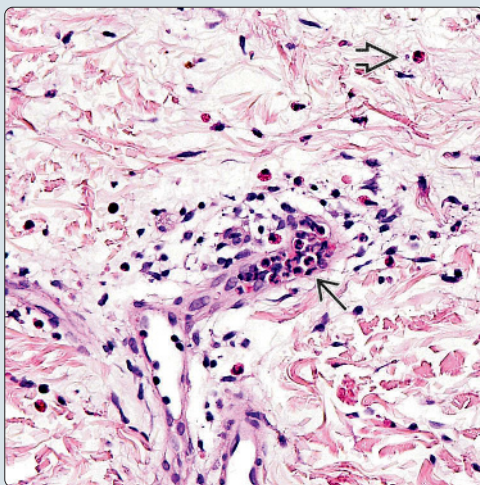


**Sparse Perivascular and Interstitial Infiltrate**

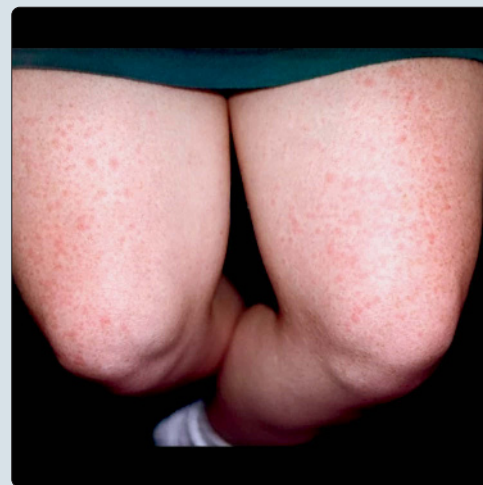


**Polymorphous Perivascular and Interstitial Infiltrate**

**(Left)** Higher power view of urticaria demonstrates neutrophils within the lumen of superficial vessels and a mild polymorphous perivascular and interstitial infiltrate, which may be the only findings in some lesions. **(Right)** Solar urticaria clinically shows symmetric pink papules and plaques over the anterior thighs. Its most important characteristic is a sharp line of demarcation where the skin is covered with clothing. Extensor extremities are a common location. (Courtesy D. Kaplan, MD.)



**Symmetric Pink Papules and Plaques of Solar Urticaria**



## TERMINOLOGY

### Synonyms

- Hives, welts, angioedema, angioneurotic edema (outdated term)

### Definitions

- Vascular reaction of skin consisting of wheals (white or red evanescent plaques) surrounded by red halo or flare and severe itching or stinging lasting 1 to several hours
- Can be classified into acute (symptoms lasting over period of < 6 weeks) and chronic (symptoms lasting over period of > 6 weeks)
- **Angioedema** is regarded as subcutaneous form of urticaria with large and deep swellings particularly affecting lips, eyelids, and genital area but may occur anywhere

## ETIOLOGY/PATHOGENESIS

### Various Associated Causes

- Most cases idiopathic but some cases associated with
  - Acute infection, allergic stimuli, such as food and drugs, aspirin, food additives, emotional stress, neoplasms, inhalants, viruses, parasites, and alcohol among others
  - When cause is known, drug is most common
  - If food is culprit, fish (especially shellfish) and nuts (especially peanuts) are most common causes
- Urticarial wheal develops as result of histamine release from mast cells, which are primary mediators of disorder
  - Release of heparin and histamine from mast cell granules leads to increased capillary permeability and extravasation of proteins and fluids
  - Mast cell degranulation also leads to recruitment of eosinophils, neutrophils, and even basophils
- Up to 1/2 of patients with chronic urticaria have autoantibodies against IgE molecule or high-affinity IgE receptor, which leads to mast cell degranulation

### Subtypes

- **Angioedema**
  - Deep form of urticaria
  - Produces edematous swelling of lips, eyelids, earlobes, skin of genitalia, or mucous membranes of oropharynx
  - Can be caused by drugs, allergies, reaction to physical agents, acquired C1-esterase inhibitor deficiency or malfunction, hypereosinophilia
- **Hereditary angioedema**
  - Due to C1-esterase inhibitor malfunction or deficiency
  - No pruritus
- **Drug-induced urticaria**
  - Most commonly caused by penicillins, NSAIDs, and sulfonamides
- **Contact urticaria**
  - Can be divided into allergic (hypersensitivity reaction) and irritant (nonimmunologically mediated)
- **Physical urticarias**
  - **Cold urticaria**
    - Usually acquired and is limited to localized sites of cooling of skin or after generalized cooling of skin
  - **Heat urticaria**
    - Much rarer than cold urticaria but has been reported in the literature

### ◦ Solar urticaria

- Patients present with wheals and pruritus at sites of sun or light exposure
- May be induced by treatment with tetracycline
- Similar to polymorphous light eruption but has faster onset and shorter duration

### ◦ Aquagenic urticaria

- Lesions appear following contact with water

### ◦ Dermatographism (factitious urticaria, dermatographia)

- Sharply localized wheal and surrounding flare within seconds to minutes of stroking skin

### ◦ Cholinergic urticaria

- Can be induced by anything that increases body temperature, such as exercise, emotional stress, hot shower or bath, or consumption of spicy foods

### ◦ Pressure or delayed pressure urticaria

- Patients develop lesions at sites of deep pressure

### • Urticaria multiforme (acute annular urticaria)

- Acute onset of transient, large, pruritic, annular, polycyclic blanchable wheals with ecchymotic centers
- Most often occurs in children aged 4 months to 4 years, and fever is usually also present
- Self-limited and typically resolves within 2-12 days

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Extremely common entity occurring in approximately 20% of the population at some point during their lifetime

### Presentation

- Presents as transient onset of erythematous or white plaques (wheals) with surrounding red halo (flare) that is often pruritic and edematous
- Can vary depending on causative agent and form of urticaria
- Can rarely present with typical skin findings plus anaphylaxis
  - Other signs of anaphylaxis include trouble swallowing and shortness of breath with wheezing
  - Hypotension and vascular collapse can ensue with sudden death

### Treatment

- Antihistamines are drugs of choice
  - For symptom relief they can be used topically (e.g., pramoxine-containing medications)
- Steroids may be required for severe cases
- Chronic recalcitrant severe disease may require more aggressive therapy
  - Combination of antihistamines from different classes of H1 blockers and H1 and H2 blockers together
  - Doxepin, sulfasalazine, more recently omalizumab
  - Immunosuppressive drugs, such as azathioprine and cyclosporine
- Treatment for urticaria associated with anaphylaxis
  - Subcutaneous epinephrine



## Prognosis

- Generally good but may have to be controlled with recurrent use of antihistamines
- May be associated with anaphylaxis, which is rarely fatal

## MICROSCOPIC

### Histologic Features

- Findings are many times nonspecific and can be quite unimpressive
- Most common findings (when present) include
  - Perivascular and interstitial dermal inflammatory infiltrate composed of eosinophils, neutrophils, and lymphocytes
    - Early lesions demonstrate sparser infiltrate typically grouped solely around blood vessels
      - Neutrophils often seen within lumina of superficial vessels (sometimes only significant finding in very early, acute lesions)
    - As lesions age, inflammatory cells extend into interstitium and with them edema and vascular dilatation ensue
  - Dermal edema (may vary from mild to severe)
    - Exemplified by separation of dermal collagen fibers
  - Dilated blood vessels and lymphatic spaces
  - Mast cells are generally not increased in number except in chronic urticaria
- **Angioedema**
  - Similar findings to urticaria with inflammatory infiltrate and edema that extends to subcutaneous tissue
- **Hereditary angioedema**
  - Subcutaneous and mucosal edema without inflammatory infiltrate

## ANCILLARY TESTS

### Serologic Testing

- Complete blood count
  - Can help rule out acute infection or other underlying illness as cause of urticaria
- C-reactive protein (CRP), although nonspecific, may be helpful to rule out active underlying systemic inflammatory process
  - Lupus, collagen vascular disease, leukemia/lymphoma, and metastatic disease can all cause urticaria and should show elevated CRP
- Antinuclear antibody
  - Can help rule out lupus erythematosus or another connective tissue disorder as cause of urticaria
- Liver function tests
  - May help elucidate underlying liver disease as cause of urticaria
- Determination of C4- or C1-esterase inhibitor levels may be helpful in diagnosing hereditary angioedema

## DIFFERENTIAL DIAGNOSIS

### Histologic

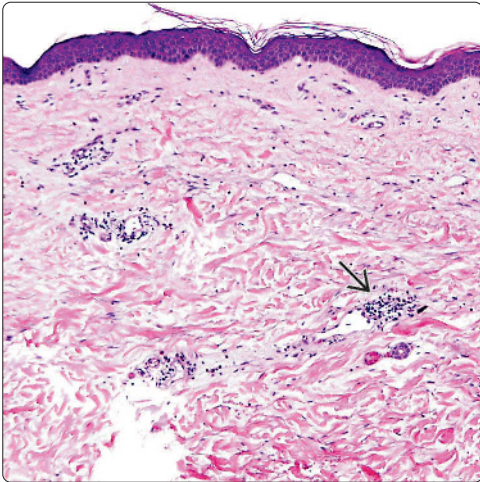
- **Arthropod bite**
  - Wedge-shaped infiltrate with epidermal disruption
  - Clinical history is important

- Inflammatory infiltrate is often much more marked and deeper than in urticaria
- Often spongiosis
- Interstitial fibrin and mucin
- **Urticarial vasculitis**
  - Rare and shows histopathologic findings of leukocytoclastic vasculitis including
    - Karyorrhexis and fibrinoid material in vessel walls (not seen in urticaria)
    - Erythrocyte extravasation is common (uncommon in urticaria)
    - Immunoreactant deposition in vessel walls by direct immunofluorescence
  - Lesions tend to last 24-72 hours and may resolve with purpura and hyperpigmentation
  - Lesions can be associated with angioedema, arthralgias, abdominal pain, and glomerulonephritis
  - Hypocomplementemia and urticarial vasculitis (~ 30% of patients) often signifies organ involvement
  - Seen in association with or preceding number of different underlying disorders including autoimmune diseases, hepatitis B and C, serum sickness, viral infections
  - **Schnitzler syndrome** is combination of urticarial vasculitis, fever, joint/bone pain, monoclonal IgM gammopathy, elevated ESR and WBC, and hepatomegaly
- **Dermatophytosis**
  - Can show many different patterns histologically
  - Can have sparse perivascular polymorphous infiltrate similar to urticaria with no other significant findings
  - Fungal forms can be seen within stratum corneum on H&E, but special stains are often helpful
    - PAS or GMS can help identify fungal forms in stratum corneum
- **Other "invisible dermatoses" or "nil diseases of skin"**
  - Many clinically obvious skin diseases may show near-normal findings on biopsy
    - Dermatophyte infection: Careful search for fungal organisms in stratum corneum or PAS stain may help
    - Cutaneous mastocytosis: Rare mast cells
    - Ichthyosis vulgaris: Absent granular layer
    - Porokeratosis: Cornoid lamellae
    - Macular amyloidosis: Hyaline deposition in papillary dermis
    - Many others including anetoderma, collagenous nevus (formerly nevus elasticus), atrophoderma, anhidrotic ectodermal dysplasia, café au lait spots, vitiligo

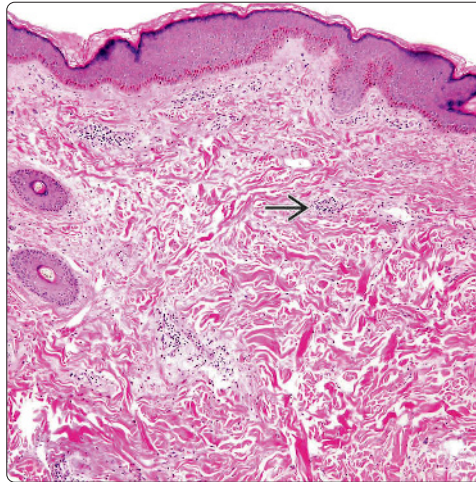
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**Perivascular and Interstitial Infiltrate of Solar Urticaria**

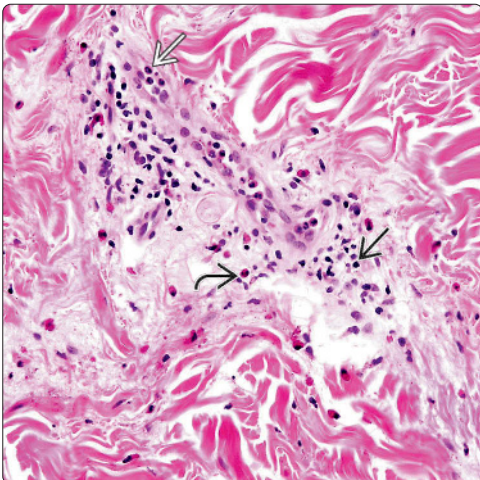


**Perivascular and Interstitial Infiltrate**

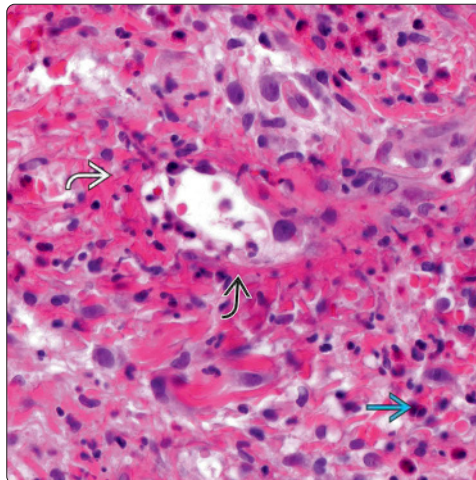


(Left) Solar urticaria histologically demonstrates a similar mild polymorphous perivascular and interstitial inflammatory infiltrate found in other clinical subtypes of urticaria. (Right) Low-power view of a case of urticaria shows a sparse perivascular polymorphous inflammatory infiltrate.

**Mixed Perivascular and Interstitial Infiltrate**

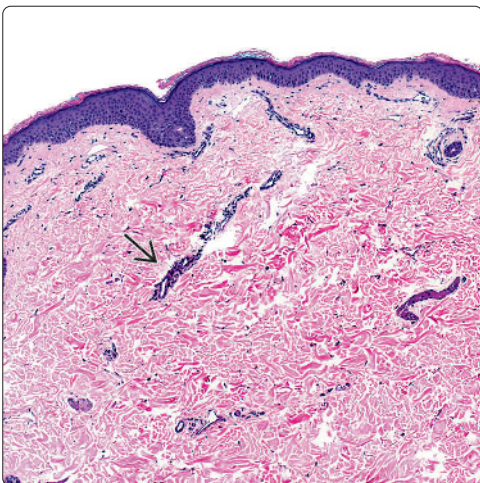


**Vessel Wall Damage in Urticarial Vasculitis**

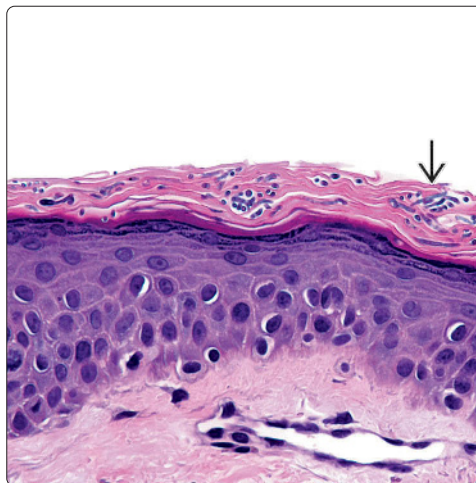


(Left) High-power view of urticaria demonstrates lymphocytes, neutrophils, and eosinophils surrounding blood vessels. (Right) Urticarial vasculitis is essentially an entity that looks like hives clinically but shows vasculitis on biopsy (seen here). Note the red blood cell extravasation, karyorrhexis, and vessel wall damage with deposition of fibrinoid material. (Courtesy D. Whittemore, DO.)

**Sparse Perivascular and Interstitial Infiltrate of Tinea Versicolor**



**Spores and Hyphae of Tinea Versicolor**



(Left) This biopsy from a patient with tinea versicolor infection also demonstrates a sparse perivascular infiltrate histologically similar to urticaria. (Courtesy T. Mulley, MD.) (Right) Higher power view of tinea versicolor demonstrates the characteristic hyphal forms in the stratum corneum that resemble spaghetti and meatballs. (Courtesy T. Mulley, MD.)



## KEY FACTS

### TERMINOLOGY

- Histologic reaction pattern denoting presence of noninflammatory small vessel thrombi

### CLINICAL ISSUES

- Can be life threatening
- Can be result of multiple underlying etiologies including
  - Warfarin or enoxaparin therapy
  - Cocaine use (retiform purpura)
  - Sepsis
  - Infection
  - Radiation
  - Atherosclerosis (cholesterol emboli)

### MICROSCOPIC

- Noninflammatory small vessel fibrin thrombi
  - Sometimes thrombi are mixed: Composed of fibrin and numerous RBCs
- Hemorrhage can be variable

- Often can find coexisting true vasculitis elsewhere on biopsy
- Ulceration, infarction, and necrosis may be present
  - Common with extensive occlusion of vessels

### TOP DIFFERENTIAL DIAGNOSES

- Leukocytoclastic vasculitis
- Calciphylaxis
- Infection (septic vasculitis)
- Embolic phenomenon (infectious or cholesterol)
- Livedo vasculopathy (atrophie blanche)
- Amyloid angiopathy

### DIAGNOSTIC CHECKLIST

- Most important determination and most valuable to clinician: Is it true vasculitis or thrombotic vasculopathy

**Warfarin-Induced Skin Necrosis**

(Left) This photograph shows a large area of painful necrosis on the leg of a patient who had been on warfarin (Coumadin) for 3 days. This is an example of warfarin-induced skin necrosis. (Right) This patient has cocaine induced retiform purpura that has evolved into complete skin necrosis and bullae formation. Levamisole contamination of the USA cocaine supply is thought to be the culprit. (Courtesy C. Stanford, MD.)

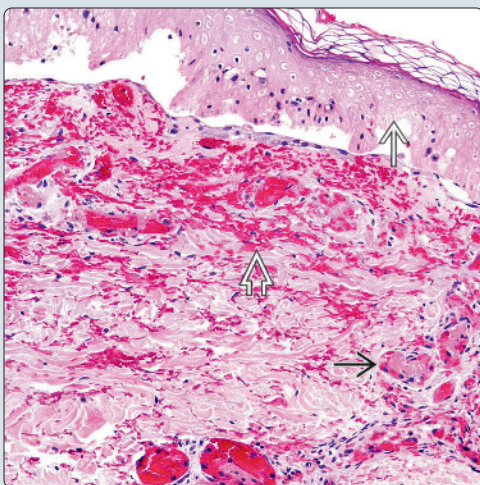


**Cocaine-Induced Skin Necrosis**

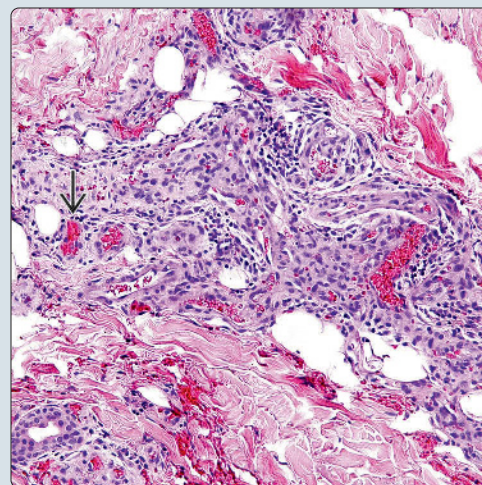


**Fibrin Thrombi With Hemorrhage**

(Left) This skin biopsy shows prominent fibrin thrombi within superficial vessels, epidermal necrosis, and prominent hemorrhage. This is an example of a thrombotic vasculopathy. (Right) This is a skin biopsy from a patient with a history of cocaine use. Note the arterioles plugged with fibrin and red blood cells.



**Thrombi With Fibrin and Red Blood Cells**





## TERMINOLOGY

### Abbreviations

- Thrombotic vasculopathy (TV)

### Synonyms

- Occlusive vasculopathy

### Definitions

- Histologic reaction pattern denoting thrombotic occlusion of small dermal vessels without associated inflammation

## ETIOLOGY/PATHOGENESIS

### Drug Exposure or Infection

- Warfarin-, heparin-, or enoxaparin-induced skin necrosis; cocaine-induced retiform purpura
- Infection
  - Ecthyma gangrenosum seen mainly in *Pseudomonas* sepsis
  - Necrotizing fasciitis seen mainly with group A  $\beta$ -hemolytic streptococci localized infection
  - *Vibrio vulnificus* sepsis from shellfish ingestion or contaminated seawater
  - *Mycobacterium ulcerans* localized infection
  - Gonococemia
- Drug exposure
  - Warfarin necrosis due to factor C or S abnormality
  - Heparin necrosis related to heparin-induced thrombocytopenia
    - Similar mechanism for enoxaparin-induced dermal necrosis
  - Cocaine-induced retiform purpura due to abuse of levamisole-contaminated cocaine

### Hypercoagulable State

- Test with hypercoagulability screen
- Antiphospholipid antibody syndrome (anticardiolipin or antilupus anticoagulant)
- Disseminated intravascular coagulopathy causing purpura fulminans (symmetrical peripheral gangrene)
- Cryoglobulinemia often associated with hypocomplementemia
- Cryofibrinogenemia
- Homocystinemia associated with defect in methylenetetrahydrofolate reductase
- Clotting factor abnormalities
  - Protein C and S deficiencies or hypofunction
  - Factor V Leiden deficiency
  - Antithrombin III deficiency

### Other Clinical Entities

- May show TV on biopsy
  - Leukocytoclastic vasculitis (LCV)
  - Livedoid vasculopathy (LV) showing atrophie blanche
  - Calciphylaxis caused by renal failure
  - Emboli associated with arterial catheterization procedures or bone fractures

### Malignancy

- May cause hypercoagulable state
- Myeloproliferative disorders

- Metastatic solid tumors

## CLINICAL ISSUES

### Presentation

- Acute cutaneous necrosis (gangrene) appears as black, indurated, well-demarcated plaques
  - Discrete multiple distal sites
    - Examples are emboli, ecthyma gangrenosum, gonococemia
  - Single proximal sites
    - Examples are purpura fulminans, calciphylaxis, warfarin necrosis
- May develop overlying bullae
- Surrounding erythema &/or induration of gangrene heralds spread of tissue necrosis
- Excruciating pain is usually present due to ischemia
- Specific features of different entities
  - Purpura fulminans
    - Presents with skin discoloration, fever, septic shock
    - Most patients younger than 7 years, but adults can be affected
    - High mortality rate (43%)
  - Warfarin-induced skin necrosis
    - Can present as purpura, maculopapular eruption, or hemorrhagic necrosis
    - Typically arises during initial few days of therapy
    - More common in obese, middle-aged women
  - Antiphospholipid antibody syndrome (APS)
    - Livedo reticularis (LR) is most common cutaneous manifestation
    - Can also see purpura, digital necrosis, skin necrosis, subungual splinter hemorrhages, and superficial venous thromboses
  - Cocaine-induced retiform purpura
    - Retiform (branching) purpuric lesions and necrosis especially involving earlobes, legs, and thighs
    - Patients usually atypical p-ANCA and anticardiolipin antibody positive
  - Cholesterol emboli
    - Cutaneous manifestations include LR, gangrene, cyanosis, ulceration, nodules, and purpura
    - Due to dislodgement of cholesterol crystals from atherosclerotic plaques
    - Occur most commonly after surgery, angiogram, trauma, or anticoagulant or thrombolytic therapy

### Treatment

- Targeted at underlying etiology and varies greatly between entities

### Prognosis

- Can be life threatening depending on etiology and underlying comorbidities

## MICROSCOPIC

### Histologic Features

- Hallmark is thrombotic occlusion of small dermal vessels without associated inflammation
- Hemorrhage can be variable
- Ulceration and infarction may be present

- Common with extensive occlusion of vessels
- Often can find coexisting true vasculitis elsewhere on biopsy
- Purpura fulminans
  - Thromboses, perivascular acute inflammatory infiltrate, endothelial swelling
- Warfarin-induced skin necrosis
  - Fibrin-platelet thrombi occlude dermal venules and arterioles with variable hemorrhage
- APS
  - Multiple deep biopsies are often required to demonstrate histopathologic changes
    - Vascular thrombi in small- to medium-sized arteries at dermal-subcutis junction or subcutis
    - Purpuric &/or necrotic skin lesions show small-vessel thrombi
  - Reactive angioendotheliomatosis can also be seen in patients with APS
    - Intravascular proliferation of endothelial cells with associated microthrombi formation
- Cocaine-related retiform purpura
  - Can look histologically identical to warfarin-induced skin necrosis
  - Fibrin-platelet thrombi in venules and arterioles in dermis and subcutis with variable hemorrhage
- Cholesterol emboli
  - Biopsy shows intravascular, biconvex, needle-shaped clefts occluding arterioles and small arteries in deep dermis and subcutis
    - Deep biopsy is important and multiple levels may be needed to demonstrate emboli
- Cryoglobulinemia
  - Eosinophilic "hyaline" thrombi in vascular lumina that stain intensely with PAS
    - Noninflammatory TV seen in ~ 10% of cases (associated vasculitis more commonly seen)

## ANCILLARY TESTS

### Serologic Testing

- Laboratory tests for underlying hypercoagulable state should be ordered by clinician
- Often divided into acquired and inherited hypercoagulable states
- For acquired hypercoagulable states the following are often ordered
  - PT, PTT, dRVVT, cardiolipin antibody (IgG and IgM), D-dimer, thrombin time, reptilase time, platelet neutralization procedure, and hexagonal phospholipid neutralization
- For inherited hypercoagulable states the following are often ordered
  - PTT, total factor VIII activity, homocysteine, prothrombin mutation, APC resistance profile, factor V Leiden functional assay, functional protein C assay, free protein S antigen, and antithrombin activity
- Specific tests ordered or recommended will vary from institution to institution

## DIFFERENTIAL DIAGNOSIS

### Leukocytoclastic Vasculitis

- True vasculitis with vessel wall damage
- Neutrophils, karyorrhexis (nuclear dust), and red blood cell extravasation
  - TV is noninflammatory
- Fibrinoid necrosis of blood vessel walls

### Calciphylaxis

- Can cause hemorrhage and painful skin ulceration mimicking vasculitis
- Seen in setting of renal failure and long-term dialysis
- Diagnosis made by histologic demonstration of calcification in small subcutaneous vessels

### Infection (Septic Vasculitis)

- Histologic findings range from paucinflammatory thromboses to authentic neutrophilic vasculitis
- Often less nuclear debris than LCV, marked hemorrhage, subepi- and intradermal pustules, and epidermal necrosis
- Causative organisms difficult to identify histologically
  - Sometimes visible on Gram-stained tissue

### Livedo Vasculopathy (Atrophie Blanche)

- Hyaline thrombi in lumina of small dermal blood vessels in upper and mid dermis
- PAS positive, diastase resistant fibrinoid material in walls of vessels and perivascular stroma
- Also associated with ulcer, dermal fibrosis, and perivascular lymphocytic infiltrates
- DIF shows fibrin in vessel walls and sometimes bands of immunoglobulin and complement deposition
- Dermal sclerosis may be seen in older lesions

### Amyloid Angiopathy

- Can be manifestation of systemic amyloidosis
- Vessel wall lumen is narrowed and replaced by amyloid (pink amorphous, Congo red-positive material)
- May also see
  - Myxoid-intimal proliferation with obliteration of lumen, aneurysm formation, and perivascular inflammatory infiltrates
  - Rarely fibrinoid necrosis and reactive angioendotheliomatosis

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**Purpura Fulminans With Symmetric Skin Necrosis**

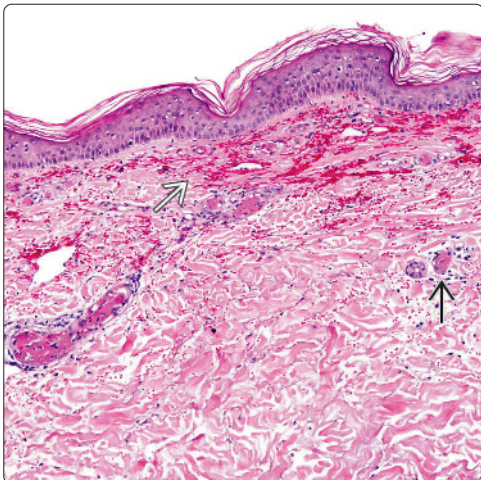


**Cocaine-Induced Retiform (Branching) Purpura**

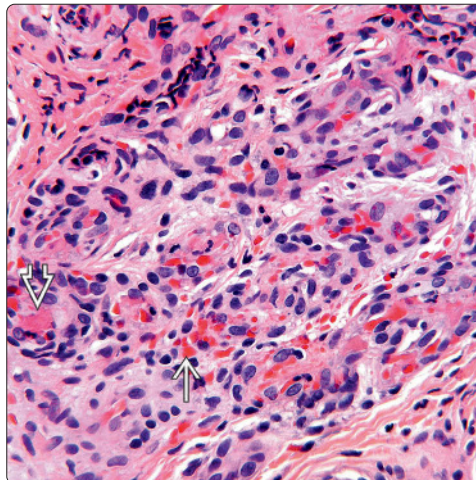


(Left) Purpura fulminans shows symmetric, widespread areas of cutaneous necrosis that appeared over days in this elderly man during chemotherapy for acute leukemia. Although this life-threatening condition is more common in infants and small children, purpura fulminans may also arise in adults. (Right) An example of cocaine-induced retiform (branching) purpura on the upper arm of a patient with a recent history of cocaine use is shown. Use of levamisole as a cutting agent has been implicated. (Courtesy C. Stanford, MD.)

**Numerous Thrombi With Hemorrhage**

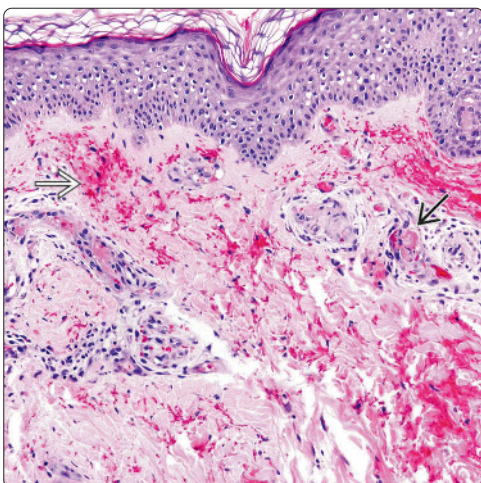


**Antiphospholipid Antibody Syndrome With Thrombi**

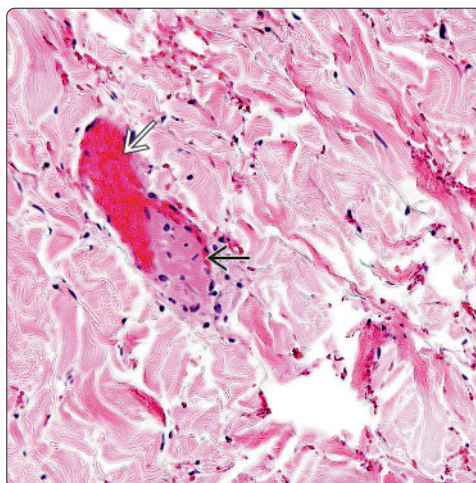


(Left) This is a skin biopsy showing obvious fibrin thrombi within superficial vessels in the dermis. Note the prominent hemorrhage present. (Right) This is a high-power view of a skin biopsy from a patient with antiphospholipid antibody syndrome. Note that fibrin can be seen here admixed with fragmented red blood cells.

**Hemorrhage and Thrombi in Thrombotic Vasculopathy**



**Mixed Thrombus: High Power**



(Left) This high-power view of a skin biopsy from a patient with a thrombotic vasculopathy shows fibrin thrombi present within the superficial vascular plexi and prominent hemorrhage. (Right) This image shows obvious fibrin and red blood cells within a vessel wall in a biopsy from a patient with a thrombotic vasculopathy. This finding necessitates close clinicopathologic correlation and, in some cases, a call to the clinician.



# Livedoid Vasculopathy

## KEY FACTS

### CLINICAL ISSUES

- Classically occurs on lower legs of middle-aged or older women

### MICROSCOPIC

- Not true vasculitis but may have sparse perivascular lymphocytic infiltrate
  - Inflammatory destruction is not seen as in leukocytoclastic vasculitis
- Early and ulcerative lesions show fibrin thrombi in lumina of small dermal blood vessels in upper and mid dermis, with fibrinoid material in vessel walls and perivascular stroma
- Later lesions show thickened and hyalinized dermal blood vessels and sometimes luminal occlusion

### TOP DIFFERENTIAL DIAGNOSES

- Stasis dermatitis with ulceration
  - May have associated ulcers but usually larger than seen in livedoid vasculopathy (LV)

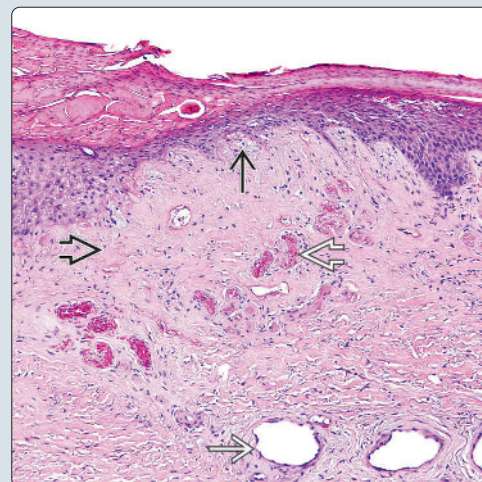
- Associated with edema and vascular insufficiency (LV is not)
  - Usually not painful (vs. LV)
- Livedo reticularis
  - Should not have vascular necrosis or ulceration
- Leukocytoclastic vasculitis
  - Prominent neutrophilic infiltration of vessels and karyorrhexis
  - Usually no thromboses
- Diabetic microvascular disease
  - May show similar eosinophilic thickening of vessels but usually no extravasation of erythrocytes
- Radiation-induced vasculitis
  - May appear similar to early stage LV but usually has stromal cellular atypia

**White Atrophic Scars of Livedoid Vasculopathy**

(Left) Characteristic healed lesions of livedoid vasculopathy present as white atrophic scars. In this patient, they were located on the back of the knee. (Right) Older lesions of livedoid vasculopathy demonstrate dilated lymphatics [E], epidermal atrophy [E], and dermal sclerosis [E]. Note the vascular luminal occlusion by fibrinoid material [E]. (Courtesy S. Florell, MD.)

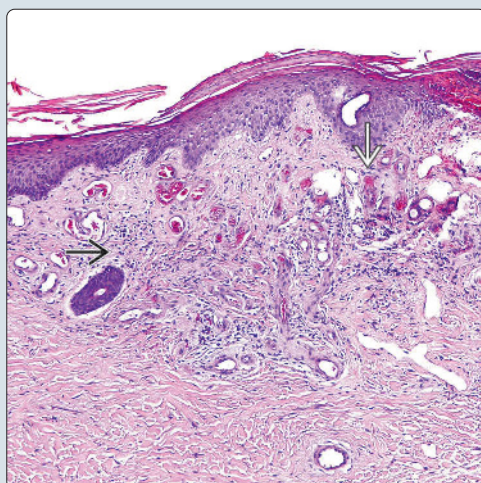


**Fibrinoid Material Occluding Vessels**

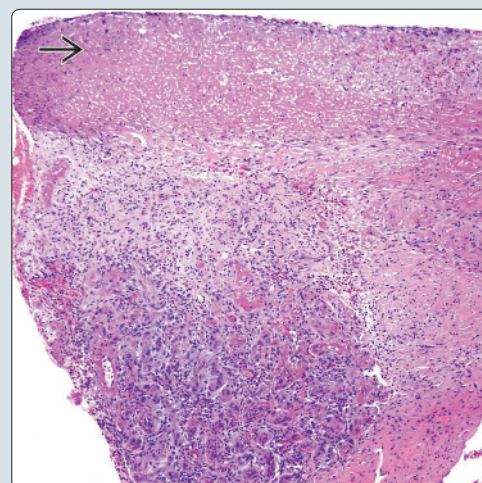


**Atrophie Blanche Older Lesion**

(Left) Another late lesion of atrophie blanche shows dermal sclerosis [E] and fibrin thrombi within vessels [E]. (Courtesy University of Utah Dermatopathology.) (Right) An older lesion of atrophie blanche demonstrates epidermal necrosis [E].



**Atrophie Blanche Older Lesion**



## TERMINOLOGY

### Abbreviations

- Livedoid vasculopathy (LV)

### Synonyms

- Livedo vasculopathy, livedo vasculitis, livedoid vasculitis, atrophie blanche, segmental hyalinizing vasculitis, painful purpuric ulcers with reticular pattern on lower extremities

### Definitions

- Hyalinizing thrombogenic vasculopathy with occlusion of small dermal vessels by fibrin thrombi and ulceration of lower extremities

## ETIOLOGY/PATHOGENESIS

### Unknown

- However, appears to be due to decreased fibrinolytic activity of blood and defective tissue plasminogen activator release from vessel walls
- Factor V Leiden mutation, heterozygous protein C deficiency, and other inherited hypercoagulable states often associated with LV

## CLINICAL ISSUES

### Epidemiology

- Age
  - Often middle age or older
  - Can affect all ages
- Sex
  - F > M

### Site

- Lower legs, especially ankles and dorsum of feet
- Rarely, extensor surface of arms or below elbows

### Presentation

- Typically presents as purpuric, telangiectatic macules and papules that eventually form punched-out, crusted ulcers that heal and form atrophic white scars
- Ulcers can recur, may be painful, and may be large and slow to heal
- Can be seasonal with greatest disease activity in winter and summer months
- Many patients have concurrent livedo reticularis

### Treatment

- Drugs
  - Low-dose aspirin and dipyridamole, or even 3rd antiplatelet drug, has been effective
  - Beraprost sodium or minidose heparin also effective
  - Psoralen plus ultraviolet A (PUVA) has been useful in some patients

### Prognosis

- Generally excellent but can be very painful

## MICROSCOPIC

### Histologic Features

- Changes vary with age of lesion
- In all stages, vascular changes are present

- Early and ulcerative lesions show fibrin thrombi in lumina of small dermal blood vessels in upper and mid dermis, with fibrinoid material in walls of vessels and perivascular stroma
  - Fibrinoid material is PAS(+), diastase resistant
  - Inflammatory destruction is not seen (vs. leukocytoclastic vasculitis) but there may be sparse perivascular lymphocytic infiltrate present
    - Hence, this disease is not true vasculitis
  - Vessels of deep dermis may be affected as well
  - Dermal sclerosis may be present if ulcer is reinvolved previous, older lesion
- Later lesions show thickened and hyalinized dermal blood vessels and possibly luminal occlusion by similar fibrinoid material
  - Fibrinoid material is seen at base and also at some distance beyond ulcers
- Even older lesions can show dermal sclerosis, scarring, epidermal atrophy, and dilated lymphatics

## ANCILLARY TESTS

### Immunofluorescence

- In early lesions, fibrin in vessel walls will be highlighted
- Later lesions may show immunoglobulins and complement in broad bands in superficial, middermal, and sometimes deep dermal vasculature
- Granular staining pattern seen if immune complex disease is not present

## DIFFERENTIAL DIAGNOSIS

### Stasis Dermatitis With Ulceration

- May have associated ulcers but usually larger than seen in LV
- Associated with edema and vascular insufficiency (LV is not)
- Usually not painful (vs. LV)
- Fibrin cuffing vessel walls in ulcer bed can resemble hyalinized vessels of LV
- White scars identical to LV may occur

### Livedo Reticularis

- Also presents as reticulated purplish macules
- Should not have vascular necrosis or ulceration

### Leukocytoclastic Vasculitis

- Prominent neutrophilic infiltration of vessels and karyorrhexis
- Usually no thromboses

### Diabetic Microvascular Disease

- May show similar eosinophilic thickening of vessels, but usually no extravasation of erythrocytes

### Radiation-Induced Vasculitis

- May appear similar to early stage LV but usually has stromal cellular atypia

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# Polyarteritis Nodosa

## KEY FACTS

### TERMINOLOGY

- Vasculitis of medium- and small-sized blood vessels
- Synonyms
  - Periarteritis nodosa, panarteritis nodosa, Kussmaul-Maier disease

### ETIOLOGY/PATHOGENESIS

- Rare: 5-10 per 1 million
- Middle age (40-60 years)
- Male > female

### CLINICAL ISSUES

- Livedo reticularis with ulcers
- Painful nodules in lower extremities
- Systemic symptoms: Weight loss, fever, heart failure, abdominal pain
- Can affect multiple internal organs and extracutaneous sites
- Chronic disease with relapses

### MICROSCOPIC

- Neutrophilic vasculitis of medium-sized cutaneous vessels in deeper dermis and subcutis
- Some lesions may have neutrophils and lymphocytes
- Often inflammation is so heavy that vessel wall is nearly obliterated

### ANCILLARY TESTS

- Verhoeff-van Gieson, elastic van Gieson
  - Both stains help highlight destruction of elastic fibers in intima and remnant of destroyed vessels

### TOP DIFFERENTIAL DIAGNOSES

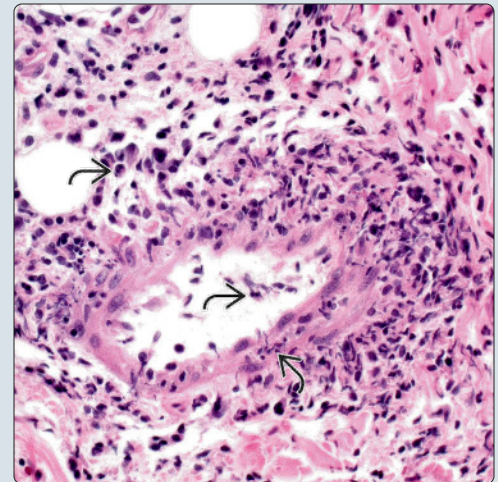
- Nodular vasculitis
- Leukocytoclastic vasculitis
- Microscopic polyangiitis
- Granulomatosis with polyangiitis (formerly Wegener)
- Churg-Strauss syndrome

### Purpuric Plaques of Polyarteritis Nodosa

(Left) Polyarteritis nodosa (PAN) presents with purpuric plaques over the lower legs and livedo reticularis over the ankle. This woman had the localized cutaneous variety. (Right) Early lesions of PAN demonstrate acute vasculitis with many neutrophils around, within, and infiltrating the arterial wall.

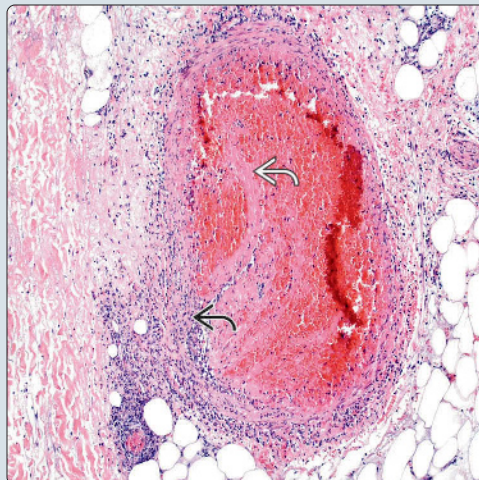


### Many Neutrophils

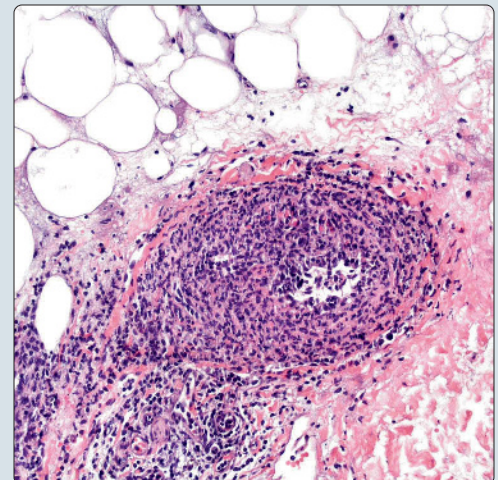


### Prominent Vasculitis

(Left) In this case of PAN, there is a focal vessel wall defect with many neutrophils and lymphocytes in this medium-sized vessel. There is also an intravascular thrombus. (Right) In this case of PAN, the vessel wall is covered by neutrophils and lymphocytes. The intima can be difficult to identify.



### Vessel Wall Obliteration





## TERMINOLOGY

### Abbreviations

- Polyarteritis nodosa (PAN)

### Synonyms

- Periarteritis nodosa
- Panarteritis nodosa
- Kussmaul-Maier disease

### Definitions

- Vasculitis of medium- and small-sized blood vessels

## ETIOLOGY/PATHOGENESIS

### Unknown Cause

- Associated with hepatitis B virus (HBV) infection
- Associated with parvovirus B19 and HIV
- Associated with other inflammatory disorders diseases
  - Lupus
  - Crohn disease
  - Rheumatoid arthritis
  - Kawasaki disease

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Rare: 5-10 per 1 million
- Age
  - Middle age (40-60 years)
- Sex
  - Male > female
- Ethnicity
  - No predilection

### Presentation

- Livedo reticularis with ulcers
- Painful nodules in lower extremities
- Systemic symptoms
  - Weight loss
  - Fever
  - Abdominal pain
  - Heart failure
- May affect vessels in extracutaneous sites and internal organs
  - May lead to organ failure

### Treatment

- Drugs
  - Systemic steroids
  - Cyclophosphamide
  - If HBV(+), use interferon-2-α and lamivudine

### Prognosis

- Chronic disease with relapses

## MICROSCOPIC

### Histologic Features

- Vasculitis of medium-sized vessels
- Early lesion
  - Edema of vessel

- Developed lesion
  - Neutrophils with lymphocytes in and around vessel wall
  - Medium-sized vessel with thrombi
- Later lesion
  - Intimal fibrosis of vessel

## ANCILLARY TESTS

### Histochemistry

- Verhoeff-van Gieson, elastic van Gieson
  - Both stains help highlight destruction of elastic fibers in intima and remnant of destroyed vessels

### Immunofluorescence

- Direct immunofluorescence shows C3 and IgM in vessel walls

## DIFFERENTIAL DIAGNOSIS

### Nodular Vasculitis

- Inflammation extend into fat lobules
- Vasculitis in both arteries **and** veins
- Inflammation predominately in subcutis
- In erythema induratum, Bazin type, lobular granulomatous panniculitis

### Leukocytoclastic Vasculitis

- Involvement of predominately superficial and small vessels
- Presence of leukocytoclasia (neutrophilic debris) and extravasated erythrocytes
- Usually in venules
- Occasionally subepidermal edema

### Microscopic Polyangiitis

- Small blood vessel (both arterioles and venules) neutrophilic vasculitis
- Predominately in superficial dermis
- Positive p-ANCA (perinuclear antineutrophil cytoplasmic antibody)

### Granulomatosis With Polyangiitis (Formerly Wegener)

- Necrotizing vasculitis with granulomas
- Foci of dermal necrosis with palisading
- Involvement of both small- and medium-sized vessels
- Positive c-ANCA (cytoplasmic antineutrophil cytoplasmic antibody)

### Churg-Strauss Syndrome

- Necrotizing vasculitis with eosinophils and granulomas
- Affect both small arteries and veins, sometimes larger vessels
- Release of eosinophilic granules
- Hypereosinophilia

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# Annular Erythemas

## KEY FACTS

### TERMINOLOGY

- Group of over a dozen clinical entities that show 1 or more variably sized erythematous patches, papules or plaques forming circles (circinate), groups of circles, or linear bands in skin

### ETIOLOGY/PATHOGENESIS

- In **EAC**, cause is often unknown
- **EMR** is most commonly manifestation of rheumatic fever
- **ECM** is caused by tickborne spirochete *Borrelia burgdorferi*
- **EGR** can occur in variety of conditions but is most notable as paraneoplastic sign of internal malignancy

### MICROSCOPIC

- **EAC** is composed of 2 types of histologic patterns
  - Superficial variant shows tight, well-demarcated, perivascular, lymphocytic, and histiocytic infiltrate often described as having coat sleeve appearance

- Deep variant often has denser inflammatory infiltrate that extends to involve deep vessels of dermis

- **ECM** shows superficial and deep perivascular infiltrate with plasma cells, macrophages, and sometimes eosinophils (often adjacent to tick bite)
- **EMR** shows superficial perivascular infiltrate composed of neutrophils, histiocytes, eosinophils, and lymphocytes
- **EGR** is somewhat nonspecific but often shows acanthosis, mild focal spongiosis, spongiosis, focal parakeratosis
- **Annular erythemas of infancy** shows superficial and deep lymphohistiocytic infiltrate with eosinophils and neutrophils occasionally

### TOP DIFFERENTIAL DIAGNOSES

- Erythema multiforme, lupus erythematosus
- Bite reactions, tinea
- Polymorphous light eruption, allergic drug reaction
- Cutaneous T-cell lymphoma

Oval Plaque With Inverse Fine Scale



*Erythema annulare centrifugum (EAC) clinically demonstrates a large, oval plaque of faint erythema and edge with inverse fine scale unattached at the inner edge. Spread is from the center and gradual over weeks to months with no itching.*

## TERMINOLOGY

### Synonyms

- Gyrate erythemas, figurate erythemas, erythema perstans group

### Definitions

- Group of over a dozen clinical entities that present with 1 or more variably sized erythematous patches, papules, or plaques forming circles (circinate), groups of circles, or linear bands in skin
  - Lesions may be fixed or migratory
  - Includes
    - **Erythema marginatum (EM)** or **erythema marginatum rheumaticum (EMR)**
    - **Erythema annulare centrifugum (EAC)**
    - **Erythema gyratum repens (EGR)**
    - **Erythema migrans**, formerly known as **erythema chronicum migrans (ECM)**
    - **Annular erythemas of infancy** (very rare)

## ETIOLOGY/PATHOGENESIS

### Varies by Type

- In EAC, cause is often unknown
  - However, has been associated with many different conditions
    - Bacterial, fungal, and viral infections
    - Drugs
    - Connective tissue and autoimmune disorders as well as many others
- EMR is most commonly manifestation of rheumatic fever
- ECM is caused by tickborne spirochete *Borrelia burgdorferi*
- EGR can occur in variety of conditions but is most notable as paraneoplastic sign of internal malignancy
  - Pathogenesis still unknown

## CLINICAL ISSUES

### Presentation

- **EAC** presents as solitary or multiple outwardly spreading erythematous, annular areas forming rings or 1/2 rings, especially affecting trunk and proximal extremities
  - Often has collarette of trailing scale
- **ECM** classically presents with small, red papule that gradually expands over days to weeks to become large, circular or annular erythema measuring 15 cm in diameter on average, sometimes with central clearing
  - Up to 1/2 of patients will develop secondary annular lesions, often multiple and smaller in size
  - Lesions may become indurated, vesicular, or even necrotic
- **EMR** gives transient and migratory macular of slightly raised annular erythema with red or pink border and pale center
- **EGR** yields striking clinical picture of undulating bands of concentric elevated erythema over entire body resembling grain of wood
- **Annular erythema of infancy** varies in clinical presentation and probably represents diverse group of annular erythemas that present in infancy
- Negative cultures and KOH for dermatophytes

- Spreading is gradual over weeks to months and not hours to days
- Almost always asymptomatic
- Removal of underlying cause should cause resolution, but waxing and waning is common
- May need biopsy to exclude cutaneous T-cell lymphoma

### Treatment

- For **EAC**, most lesions eventually subside, although, topical steroids can be used
- **ECM** can be treated with doxycycline or amoxicillin
- **EMR** resolves with treatment of rheumatic fever
- Treatment of underlying neoplasm can cause dramatic improvement and even complete resolution of lesions of **EGR**

### Prognosis

- Excellent for all types with exception of **EGR**
  - Prognosis for **EGR** varies depending on associated underlying malignancy

## MICROSCOPIC

### Histologic Features

- **EAC** is composed of 2 types of histologic patterns
  - Superficial variant shows tight, well-demarcated perivascular lymphocytic and histiocytic infiltrate often described as having coat sleeve appearance
    - Inflammatory infiltrate confined to upper or superficial dermis and eosinophils may rarely be seen
    - Superficial blood vessels often dilated
    - Focal spongiosis and parakeratosis present in some cases
  - Deep variant often has denser inflammatory infiltrate that extends to involve deep vessels of dermis
    - Spongiosis and parakeratosis are often absent
- **ECM**
  - Shows superficial and deep perivascular infiltrate with plasma cells, macrophages, and sometimes eosinophils (often adjacent to tick bite)
  - Rare cases may show interface change, neutrophils and eosinophils, only superficial lymphocytic infiltrate, &/or sometimes complete absence of plasma cells
  - Warthin-Starry silver stain can identify organism in up to 1/2 of cases
- **EMR**
  - Biopsy shows superficial perivascular infiltrate composed of neutrophils, histiocytes, eosinophils, and lymphocytes
  - Should be no evidence of true vasculitis
  - Neutrophil microabscesses sometimes seen
- **EGR**
  - Findings are somewhat nonspecific but often show acanthosis, mild focal spongiosis, and focal parakeratosis
  - Superficial perivascular lymphohistiocytic infiltrate occasionally with eosinophils in variable numbers
  - Clinical appearance is so distinctive, biopsy is rarely necessary
    - Biopsy may be performed to rule out odd presentation of cutaneous T-cell lymphoma
  - Direct immunofluorescence shows granular IgG and C3 along basement membrane zone
- **Annular erythemas of infancy**



# Annular Erythemas

- Most often superficial and deep lymphohistiocytic infiltrate with eosinophils and neutrophils occasionally

## ANCILLARY TESTS

### Immunofluorescence

- Direct immunofluorescence for **EGR** shows granular IgG and C3 along basement membrane zone

### PCR

- If serologic testing is negative and Lyme disease is still suspected or patient may be immunocompromised
  - Borrelia* species DNA detection by PCR may be indicated

### Serologic Testing

- When diagnosis is in doubt, classic **EM** is not present, or tick exposure or bite is questionable
  - B. burgdorferi* antibodies total by ELISA or IgG and IgM antibodies by Western blot can be helpful
  - If known tick bite and **erythema migrans** present, no need for ancillary testing and treatment should be initiated

## DIFFERENTIAL DIAGNOSIS

### Histological

- Erythema multiforme**
  - Necrotic keratinocytes usually prominent
  - Lymphocyte exocytosis
  - Interface dermatitis
- Bite reactions**
  - ECM can sometimes show indistinguishable pattern
  - Warthin-Starry silver stain can sometimes demonstrate spirochetes
  - Clinical history and adjunct studies, such as serologic studies, polymerase chain reaction, or monoclonal antibody often required to differentiate etiologic causes
- Lupus erythematosus**
  - Interface changes usually present
  - Thickened basement membrane; may have epidermal atrophy
  - Follicular plugging
  - Immunofluorescence will reveal granular deposits of IgM, IgG, and complement at dermal-epidermal junction
- Polymorphous light eruption**
  - Pattern of dermal inflammation can be very similar
  - Typically has papillary dermal edema (may be marked)
  - Typically contains neutrophils vs. EAC, EM, and EGR
  - Direct immunofluorescence demonstrates perivascular IgM and C3 deposition
- Allergic drug reaction**
  - Perivascular pattern of inflammation, similar to annular erythemas
  - Numerous eosinophils are more characteristic of drug eruption, but eosinophils may be seen in annular erythemas
  - Drug reactions with this histology are more commonly morbilliform, rather than annular
  - Medication history may assist in confirming diagnosis

### Clinical

- Urticaria**
  - Evanescent: < 24 hours

- Granuloma annulare**
  - Over joints, usually in older children and young adults
  - Granulomatous histology
  - Not evanescent over hours but instead over months to years
  - Histology characteristic
- Tinea corporis**
  - Border scaling, crusted or vesicular
  - Pruritic
  - Positive KOH and culture
- Erythema multiforme**
  - Targetoid patches and plaques with red or purple macular center (bull's eye), in contrast to central clearing of annular erythemas
  - Lacks characteristic scale of EAC
- Elastosis perforans serpiginosa**
  - Usually able to see individual papules making up border
  - Not evanescent
- Nummular eczema**
  - Exquisite pruritus
  - Surface oozing, crusted or vesicular
- Cutaneous T-cell lymphoma**
  - Not evanescent
  - Usually no scale on edge
  - Histology characteristic
  - May be associated with lymphadenopathy and underlying systemic lymphoma
  - May ulcerate as disease progresses
- Discoid lupus erythematosus**
  - Wide variations in color
  - Scar formation common
  - Prefers scalp, face, ears
  - Histology characteristic including direct immunofluorescence
  - Flares with sun exposure
  - Follicular plugging may be apparent

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**Wood Grain Appearance of Erythema Gyratum Repens**

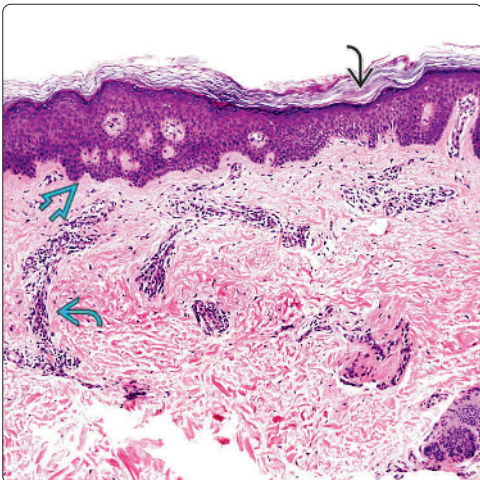


**Large Oval Pink Plaque of Erythema Chronicum Migrans**

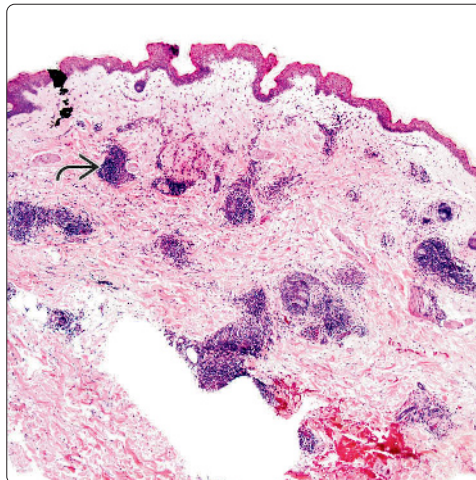


(Left) This is erythema gyratum repens (EGR) over the trunk of a man with a characteristic wood grain appearance. Clinical appearance is distinct, but a biopsy may be performed to rule out CTCL. (Right) ECM on the posterior thigh in a patient with Lyme disease presents as a large, oval, pink plaque characteristic for the lesion (central clearing is not always present). Generalized malaise and skin disease dissipated within 48 hours of starting oral doxycycline. (Courtesy PMPH-USA Publishing.)

**Superficial Perivascular Lymphohistiocytic Infiltrate**

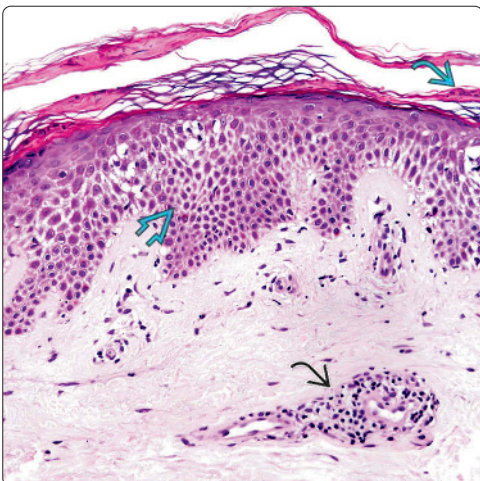


**Superficial and Deep Tight Perivascular Inflammation**

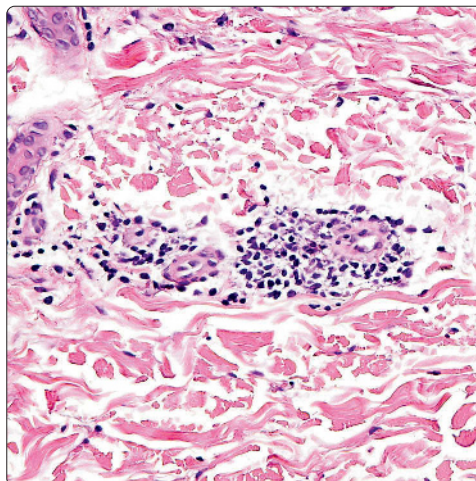


(Left) Biopsy findings in EGR are nonspecific but often include focal parakeratosis [2], a superficial perivascular lymphohistiocytic infiltrate [2], and acanthosis [2]. (Courtesy M. McCollough, MD.) (Right) This biopsy shows characteristic features of a deep gyrate erythema with superficial and deep tight perivascular inflammation [2].

**Lymphocytic Cuffing of Vessels and Spongiosis**



**Coat Sleeve Lymphocytes**



(Left) High-power view of EAC demonstrates superficial perivascular lymphocyte cuffing [2], giving a characteristic coat sleeve appearance. Focal spongiosis [2] and parakeratosis [2] may be seen in some cases. (Right) Higher power image shows the tight perivascular coat sleeve lymphocytes.



# Giant Cell Arteritis

## KEY FACTS

### TERMINOLOGY

- Systemic granulomatous vasculitis of medium and large-sized arteries

### ETIOLOGY/PATHOGENESIS

- Both environmental and genetic factors are thought to play role
- Refractory giant cell arteritis is sometimes due to varicella-zoster virus, particularly in patients who are immunocompromised or taking corticosteroids

### CLINICAL ISSUES

- Epidemiology
  - Patients usually > 50 years, usually women
  - Highest rates in Caucasians of Northern European decent
- Usually presents with
  - Temporal headaches, fever, anemia, elevated erythrocyte sedimentation rate

- May lead to
  - Claudication of tongue or jaw muscles
  - Stroke, vision loss, aortic aneurysm, skin ulceration and necrosis
- Temporal artery most frequently and consistently effected

### MICROSCOPIC

- Thickened intimal layer with narrowing of lumen
- Granulomatous inflammatory infiltrate within arterial wall
  - CD4(+) T cells, macrophages, multinucleated giant cells, ± eosinophils
- Disruption of internal elastic lamina
- Discontinuous lesions

### TOP DIFFERENTIAL DIAGNOSES

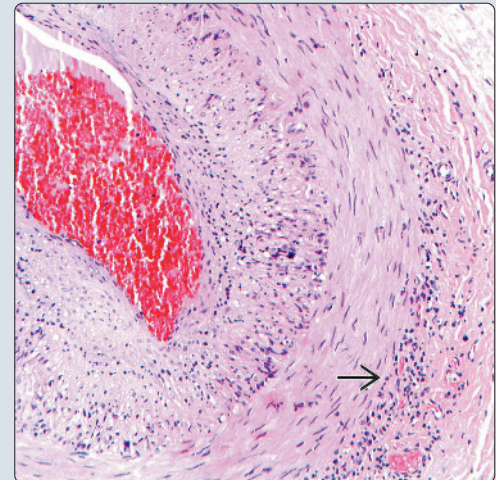
- Granulomatosis with polyangiitis (Wegener granulomatosis)
- Takayasu arteritis
- Churg-Strauss syndrome
- Lymphomatoid granulomatosis

### Skin Ulceration and Necrosis

(Left) Giant cell arteritis presents in this patient with ulceration and necrosis of the temporal scalp. (Right) At high power, the chronic inflammatory infiltrate consists of lymphocytes with virtually no histiocytic component.

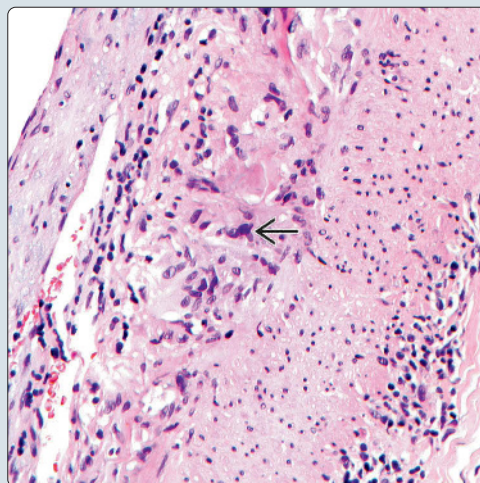


### Mild Chronic Inflammation

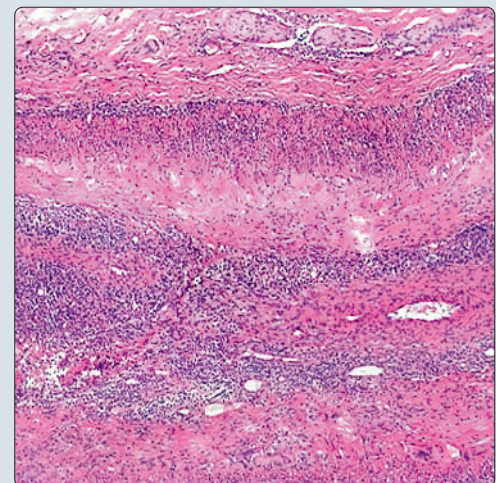


### Multinucleated Giant Cells

(Left) In classic lesions, the arterial wall is infiltrated in part by histiocytes and multinucleated giant cells. This feature is not universally present. (Right) Temporal arteritis with an intense chronic and histiocytic inflammatory infiltrate causing thickening of the vessel wall and occlusion of the arterial lumen.



### Florid Inflammation in Some Cases





## TERMINOLOGY

### Abbreviations

- Giant cell arteritis (GCA)

### Synonyms

- Temporal arteritis, cranial arteritis

### Definitions

- Systemic granulomatous vasculitis of medium and large-sized arteries
  - Primarily affects large arteries branching from aorta
    - Especially extracranial branches of carotid artery, such as temporal artery

## ETIOLOGY/PATHOGENESIS

### Etiology

- Unknown
- Both environmental and genetic factors may play role
- Refractory GCA is sometimes due to varicella-zoster virus, particularly in patients who are immunocompromised or taking corticosteroids

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - 15-25 in 100,000
- Age
  - > 50 years
- Sex
  - Affects mostly women
- Ethnicity
  - Highest rates in Caucasians of Northern European decent

### Site

- Temporal artery most frequent

### Presentation

- Usually presents with
  - Headaches located over temporal region
  - Fever, anemia, elevated erythrocyte sedimentation rate
  - Claudication of tongue or jaw muscles
  - Stroke
  - Partial or complete vision loss
  - Tongue infarction
  - Aortic aneurysm
- Most common dermatological findings are tenderness of temporal area and scalp ± necrosis and ulceration
- Polymyalgia rheumatica occurs in ~ 40% of patients with GCA
  - Characterized by aching of shoulder and hip girdle with morning stiffness

### Treatment

- Drugs
  - Corticosteroids are standard therapy and bring about rapid clinical response within 48 hours
  - Methotrexate has had mixed results in clinical trials
  - Aspirin is recommended to prevent ischemic events associated with GCA

## MICROSCOPIC

### Histologic Features

- Intense inflammatory infiltrate within arterial wall
  - Thickened intimal layer
  - May have nearly complete occlusion of arterial lumen
- Granulomatous mononuclear inflammatory infiltrate
  - Composed of CD4(+) T cells, activated macrophages, and eosinophils
    - Multinucleated giant cells are present in only 50% of biopsies
- Disruption of internal elastic lamina
- Discontinuous lesions

## ANCILLARY TESTS

### Histochemistry

- Elastic van Gieson
  - Positive in elastic fibers: Visualize disruption

## DIFFERENTIAL DIAGNOSIS

### Granulomatosis With Polyangiitis (Wegener Granulomatosis)

- Granulomatous arteritis involving upper and lower respiratory system and kidneys
- Necrotizing vasculitis
- May involve temporal artery
  - Respiratory &/or renal involvement should be present
- Primarily small and medium-sized arteries are involved

### Takayasu Arteritis

- Granulomatous arteritis of aortic arch
- Leads to absent pulses in upper extremities
- Associated with erythema nodosum, pyodermatous ulcers, rashes, necrotizing vasculitis, and urticaria

### Churg-Strauss Syndrome

- Granulomatous vasculitis
  - Necrotizing vasculitis, tissue infiltration by eosinophils, extravascular granulomas
- 4 of 6 features must be present
  - Peripheral eosinophilia ≥ 10%, asthma, paranasal sinusitis, pulmonary infiltration, vasculitis, mononeuritis multiplex

### Lymphomatoid Granulomatosis

- Primarily pulmonary involvement but may be extrapulmonary
- Skin manifestations may be initial manifestation
- Necrotizing vasculitis with mixed infiltrate
- Occlusion of involved vessels with necrosis

## SELECTED REFERENCES

1. Gilden D et al: Widespread arterial infection by varicella-zoster virus explains refractory giant cell arteritis. *Neurol Neuroimmunol Neuroinflamm*. 2(4):e125, 2015
2. Glaser J et al: Using temporal artery biopsy to diagnose giant cell arteritis in a patient with bilateral arm ischemia. *Int J Surg Case Rep*. 13:95-8, 2015
3. Ponte C et al: Giant cell arteritis: current treatment and management. *World J Clin Cases*. 3(6):484-94, 2015
4. Davies CG et al: The role of temporal artery biopsies in giant cell arteritis. *Ann R Coll Surg Engl*. 93(1):4-5, 2011

# Pruritic Urticarial Papules and Plaques of Pregnancy

## KEY FACTS

### TERMINOLOGY

- Extremely pruritic eruption of papules and urticarial plaques most often of primigravidas during their 3rd trimester of pregnancy

### CLINICAL ISSUES

- Actually quite common (estimated at 1 in 200 pregnancies)
- Most common gestational dermatosis
- Lesions typically begin in abdominal striae (stretch marks) and usually spare periumbilical area
  - Then spreads to abdomen, buttocks, thighs, and extremities

### MICROSCOPIC

- Lymphohistiocytic perivascular infiltrate involving papillary dermis and often extending to middermis
- Eosinophils are present in variable numbers in perivascular and interstitial distribution

- Direct immunofluorescence shows no in situ immunoreactants

### TOP DIFFERENTIAL DIAGNOSES

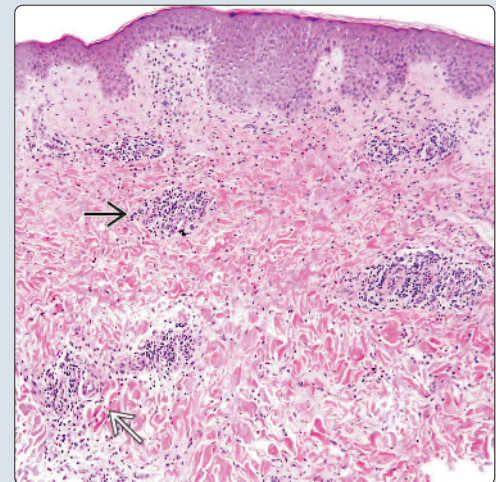
- Herpes (pemphigoid) gestationis
  - Histologic differentiation from pruritic urticarial papules and plaques of pregnancy (PUPPP) difficult
  - Direct immunofluorescence positive for C3 in epidermal basement membrane
- Urticaria
  - Histologically often indistinguishable
  - Evanescient, does not necessarily begin in stretch marks or during pregnancy
- Contact dermatitis
  - Older lesions of PUPPP may appear very similar histologically
  - Frequently linear, blisters more common
- Arthropod bite reaction
  - Clinical history and context important

(Left) Pruritic urticarial papules and plaques of pregnancy (PUPPP) presents as urticarial intensely pruritic pink papules that may form plaques that can become confluent and cover the entire thigh as shown in this primigravida. (Right) Low-power view of PUPPP demonstrates a lymphohistiocytic perivascular infiltrate in the papillary dermis and even extending to the middermis.

Intensely Pruritic Urticarial Pink Papules

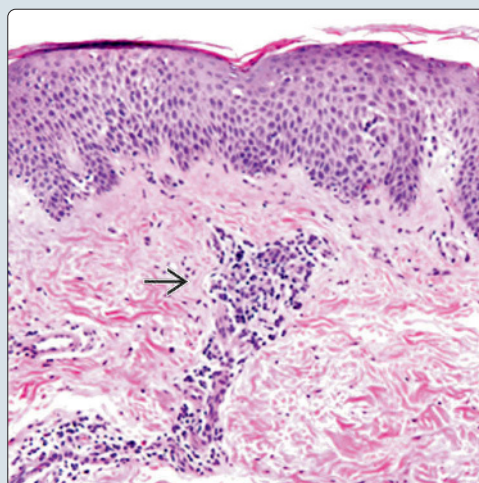


Lymphohistiocytic Perivascular Infiltrate

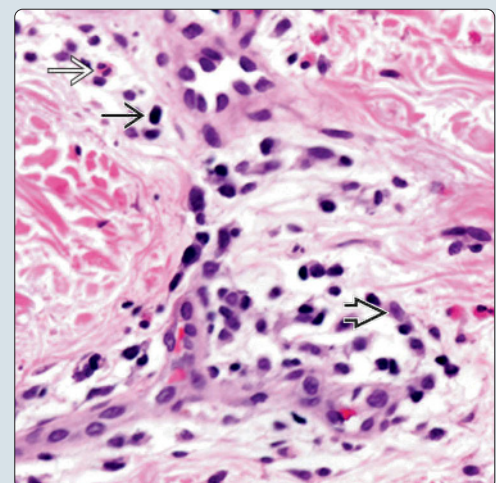


(Left) Another example of PUPPP demonstrates a perivascular lymphohistiocytic infiltrate in the papillary dermis, along with spongiosis. (Right) High-power view of the perivascular infiltrate in PUPPP reveals numerous lymphocytes, histiocytes, and occasional eosinophils.

Perivascular Lymphohistiocytic Infiltrate With Spongiosis



Lymphocytes, Histiocytes, and Eosinophils



## TERMINOLOGY

### Abbreviations

- Pruritic urticarial papules and plaques of pregnancy (PUPPP)

### Synonyms

- Polymorphic eruption of pregnancy
- Late onset prurigo of pregnancy

### Definitions

- Extremely pruritic eruption of papules and urticarial plaques most often of primigravidas during their 3rd trimester of pregnancy

## ETIOLOGY/PATHOGENESIS

### Unknown

- However, there has been association noted with excessive maternal weight gain

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Actually quite common (estimated at 1 in 200 pregnancies)
  - Most common gestational dermatosis

### Site

- Lesions typically begin in abdominal striae (stretch marks) and usually spare periumbilical area
  - Then spreads to abdomen, buttocks, thighs, and extremities

### Presentation

- Intensely pruritic eruption with onset most commonly in primigravidas in 3rd trimester
  - Usually begins in stretch marks as typical urticaria-like pink papules
  - As it spreads over trunk and extremities to become plaques, evanescence is not noticed
- In 1 study, > 1/2 of patients developed other features later during their course including
  - Erythema, vesicles, targetoid, and eczematous lesions
- Curious increase in incidence in twin pregnancies

### Treatment

- Topical steroids or occasionally systemic corticosteroids in more severe cases

### Prognosis

- Fetal and maternal outcomes are not affected by disease
- Eruption resolves with delivery or cessation of breast feeding
- Usually does not recur with subsequent pregnancies
- Newborns may rarely manifest transient lesions
- Rarely begins postpartum, does not resolve after delivery, and recurs with estrogens including birth control pills

## MICROSCOPIC

### Histologic Features

- Lymphohistiocytic perivascular infiltrate involving papillary dermis and often extending to middermis
- Occasional eosinophils are common in dermal infiltrate (sometimes very few)
  - Rare variant with numerous interstitial eosinophils or even eosinophil-rich subepidermal blistering has been reported
- Perivascular or dermal edema may also be present
- ~ 1/3 of cases may show spongiosis, parakeratosis, scales, or crust in epidermis
  - Spongiotic vesiculation sometimes characterizes later lesions
- Immunofluorescence is almost always negative
  - Nonspecific immunoreactants surrounding vessels and near dermal-epidermal junction have been reported in some cases

## DIFFERENTIAL DIAGNOSIS

### Herpes (Pemphigoid) Gestationis

- Histologic differentiation from PUPPP difficult
- Direct immunofluorescence positive for C3 in epidermal basement membrane
- Clinically
  - Periumbilical lesions, tend to spare striae
  - Acute exacerbations immediately following delivery
  - Persistence > 3 weeks postpartum
  - Systemic corticosteroids almost always required

### Urticaria

- Histologically often indistinguishable
- Evanescent, does not necessarily begin in stretch marks or during pregnancy

### Contact Dermatitis

- Older lesions of PUPPP may appear very similar histologically
- Frequently linear, blisters more common

### Arthropod Bite Reaction

- Acute lesions can appear very similar with mild to moderate polymorphous perivascular infiltrate
- Mouthparts may be seen
- Sometimes tract of necrosis on either side
- Clinical history and context important

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# Granulomatosis With Polyangiitis

## KEY FACTS

### CLINICAL ISSUES

- Correlation of clinical and histologic (most commonly LCV) findings with ANCA serology (most often PR3/c-ANCA positivity) can allow for diagnostic findings of granulomatosis with polyangiitis (GPA) in most cutaneous lesions
- Cutaneous manifestations occur in ~ 14-50% of patients
- Cutaneous lesions are more likely to develop in patients with multiorgan involvement
- Cutaneous lesions may precede, develop concurrently with, or develop after systemic disease
- Cyclophosphamide in combination with steroids is treatment of choice

### MICROSCOPIC

- Findings can be quite nonspecific (50% of cases in 1 study) with only ~ 20% of cases showing classic necrotizing, granulomatous vasculitis

- Leukocytoclastic vasculitis is very common finding in skin biopsies
- In diagnostic lesions
  - Vascular changes showing pyknotic neutrophils with fibrinoid deposits in vessel walls (necrotizing angiitis) of small- and medium-sized dermal vessels are typically present
    - Red cell extravasation is typically also present
- Older lesions may show palisading extravascular granulomas
  - Giant cells commonly seen in granulation tissue or scattered throughout chronic nonspecific inflammation

### ANCILLARY TESTS

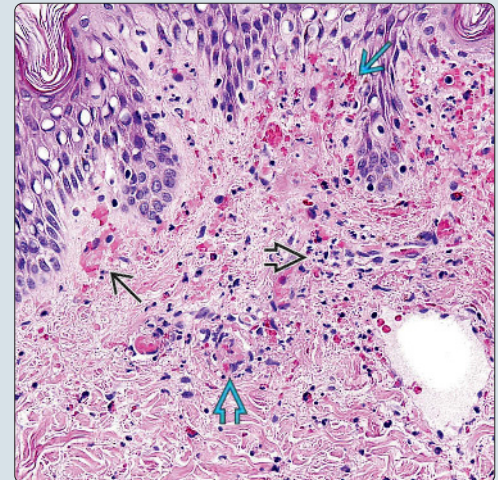
- PR3/c-ANCA is positive in 75-90% of patients with active/systemic GPA and is considered highly sensitive in detecting active, systemic disease
- Lack of PR3/c-ANCA positivity cannot exclude disease

### Gangrenous Lesions

(Left) Early gangrenous changes of the digits on the hand are present here secondary to granulomatous vasculitis of granulomatosis with polyangiitis (GPA). (Right) This biopsy of cutaneous GPA shows extravascular fibrinoid material [E], karyorrhexis [E], RBC extravasation [E], and fibrinoid necrosis of vessels [E]. (Courtesy K. Duffy, MD.)

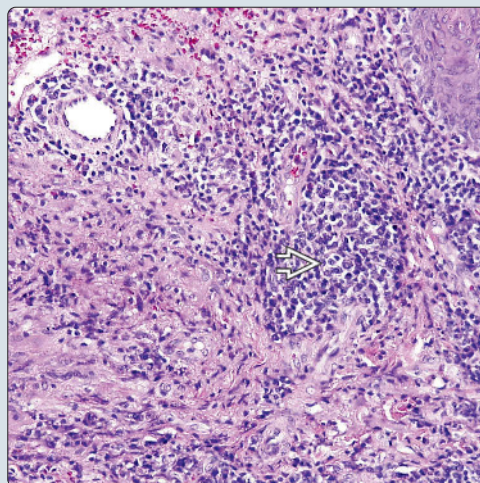


### Leukocytoclastic Vasculitis

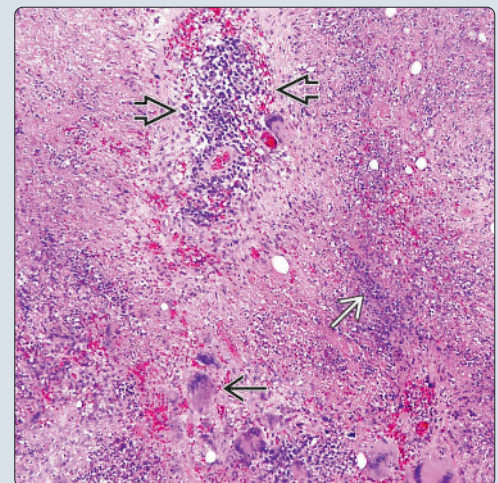


### Plasma Cells

(Left) Cases of GPA may also have a significant plasma cell [E] infiltrate in addition to leukocytoclastic vasculitis. (Right) Classic sinonasal GPA (rarely seen in skin biopsies) shows giant cells [E], blue granular necrotic material [E], and evidence of vessel wall destruction [E]. (Courtesy G. Ellis, DDS.)



### Inflammation and Vessel Destruction



## TERMINOLOGY

### Abbreviations

- Granulomatosis with polyangiitis (GPA)

### Synonyms

- Wegener granulomatosis

### Definitions

- Systemic disease characterized by generalized necrotizing angitis of medium-sized blood vessels, necrotizing granulomas of upper and lower respiratory tract, and focal necrotizing glomerulonephritis

## CLINICAL ISSUES

### Presentation

- Cutaneous manifestations occur in ~ 14-50% of patients
- May precede, develop concurrently with, or develop after, systemic disease
- Cutaneous lesions are more likely to develop in patients with multiorgan involvement

### Treatment

- Cyclophosphamide in combination with steroids is treatment of choice

### Prognosis

- Before treatment, mean survival was 5 months after diagnosis with 90% mortality by 2 yr
- Most patients respond well to cyclophosphamide treatment
  - However, flare-ups as well as long-term complications such as hearing loss, deafness, and chronic renal failure can still occur in treated patients

## MICROSCOPIC

### Histologic Features

- Findings can be quite nonspecific (50% of cases in 1 study)
- Classic finding of necrotizing, granulomatous vasculitis actually appears to involve only minority of cases (ranging from 0-20% of skin biopsy specimens)
- Leukocytoclastic vasculitis (LCV) is very common finding in skin biopsies
  - 1 study showed LCV present in 80% of cutaneous lesions in patients with GPA
  - However, nonspecific chronic inflammation is also very common finding
- In diagnostic lesions
  - Vascular changes showing pyknotic neutrophils with fibrinoid deposits in vessel walls (necrotizing angitis) of small- and medium-sized dermal vessels are typically present
    - Red cell extravasation is typically also present
  - Extravascular changes including foci of necrosis, fibrinoid degeneration, neutrophils, &/or karyorrhexis may be present
- Older lesions may show palisading extravascular granulomas
  - Giant cells commonly seen in granulation tissue or scattered throughout chronic nonspecific inflammation

## ANCILLARY TESTS

### Serologic Testing

- PR3/c-ANCA is positive in 75-90% of patients with active systemic GPA and is considered highly sensitive in detecting active systemic disease
  - However, MPO/p-ANCA can be seen in ~ 10% of patients with GPA
- Lack of PR3/c-ANCA positivity cannot exclude disease
  - 40% of patients with limited GPA and 10-25% of patients with active systemic GPA may be ANCA negative

## DIFFERENTIAL DIAGNOSIS

### Microscopic Polyangiitis

- Essentially diagnosis of exclusion
  - Does not have pulmonary granulomatous inflammation once clinical manifestations develop
- Early cutaneous GPA can be microscopically indistinguishable from microscopic polyarteritis until respiratory symptoms occur

### Churg-Strauss Syndrome

- Marked eosinophilia is typically present
- If only granulomas and allergic vasculitis are present, histologic differentiation may be impossible
- Does not show granulomatous vasculitis; instead typically has extravascular granulomas

### Leukocytoclastic Vasculitis

- May be feature of GPA
- Remember LCV is simply reaction pattern to wide range of underlying disorders
- Should not have granulomatous respiratory tract involvement
- Vasculitis is not granulomatous

### Polyarteritis Nodosa

- No respiratory tract involvement
- Less granulomatous inflammation

### Lymphomatoid Granulomatosis

- No respiratory tract involvement
- Atypical, CD56 positive lymphocytes
- Less granulomatous inflammation

### IgG4-Related Disease

- Fibroinflammatory disease effecting multiple organ systems
- May clinically mimic GPA due to involvement around vessels
- GPA does not have increased IgG4 plasma cells or elevated serum IgG4

## SELECTED REFERENCES

1. Hazebroek MR et al: Prevalence and prognostic relevance of cardiac involvement in ANCA-associated vasculitis: eosinophilic granulomatosis with polyangiitis and granulomatosis with polyangiitis. *Int J Cardiol.* 199:170-179, 2015
2. Ikeda S et al: Comparative investigation of respiratory tract involvement in granulomatosis with polyangiitis between PR3-ANCA positive and MPO-ANCA positive cases: a retrospective cohort study. *BMC Pulm Med.* 15:78, 2015



## KEY FACTS

### TERMINOLOGY

- Idiopathic systemic necrotizing vasculitis of small- to medium-sized arteries with eosinophil-rich granulomatous inflammation of respiratory tract and eosinophilia in patients with preexisting asthma and allergic rhinitis

### CLINICAL ISSUES

- Necrotizing vasculitis and asthma almost always present
  - Can occur simultaneously, but asthma typically precedes vasculitic lesions
- Although upper respiratory tract and pulmonary involvement is most common, cutaneous lesions can be seen in 40-70% of patients
- Cutaneous lesions can vary from distinctive nodules, papules, vesicles, petechiae, erythema, or ulceration

### MICROSCOPIC

- 3 main histologic features are usually present




- Leukocytoclastic vasculitis (LCV) involving postcapillary venules plus arterioles
- Tissue infiltration with eosinophils
- Extravascular granulomas or Churg-Strauss granulomas with fibrinoid or eosinophilic central necrosis

### TOP DIFFERENTIAL DIAGNOSES

- LCV
- Polyarteritis nodosa (PAN)
- Granulomatosis with polyangiitis (GPA)

### DIAGNOSTIC CHECKLIST

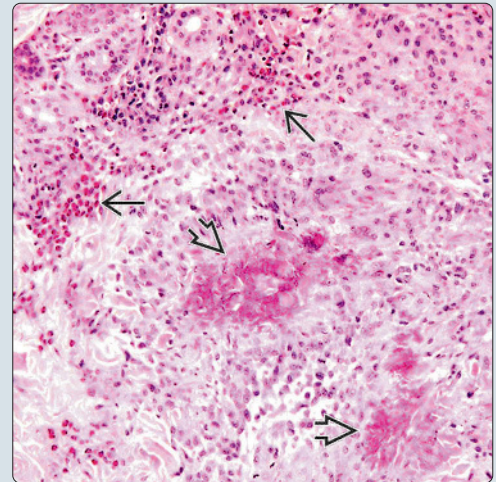
- Churg-Strauss syndrome (CSS), GPA, and PAN can have clinical and histologic overlap, but it does appear that they all represent distinct entities
- Histologic findings in CSS are not pathognomonic
- Careful clinical clinicopathologic correlation is recommended to establish correct diagnosis





(Left) The elbow in this patient with Churg-Strauss syndrome (CSS) demonstrates multiple erythematous papules with depressed central crusts . (Right) Skin biopsy from CSS demonstrates numerous eosinophils  and extravascular eosinophilic palisaded granulomas .

Erythematous Papules With Central Crusts

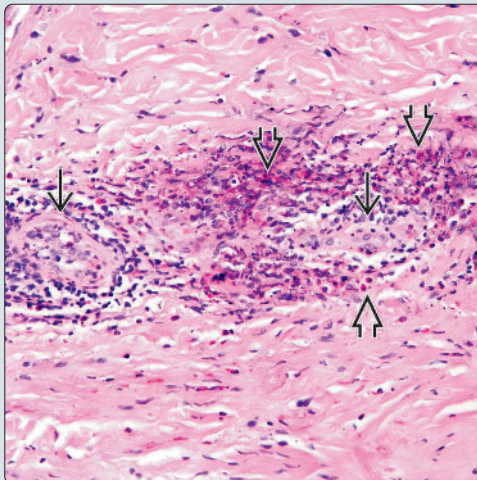


Eosinophils and Eosinophilic Palisaded Granulomas

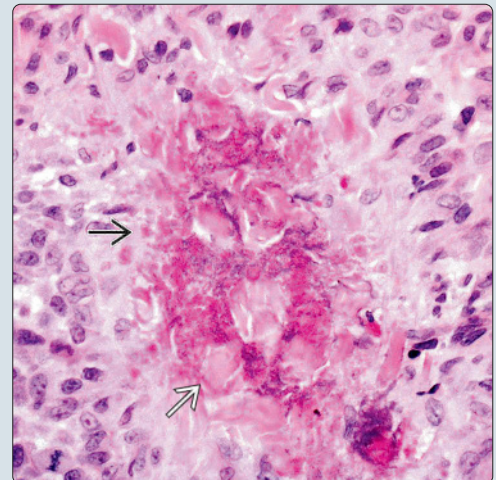


(Left) High-power view demonstrates characteristic necrotizing vasculitis  of small dermal vessels and numerous eosinophils  in cutaneous CSS. (Right) High-power view of CSS shows an extravascular eosinophilic and slightly basophilic granuloma  with entrapped collagen .

Necrotizing Vasculitis



Extravascular Eosinophilic Granuloma





## TERMINOLOGY

### Abbreviations

- Churg-Strauss syndrome (CSS)

### Synonyms

- Allergic granulomatosis, allergic granulomatosis with angiitis, necrotizing angiitis with granulomata

### Definitions

- Idiopathic systemic necrotizing vasculitis of small- to medium-sized arteries with eosinophil-rich granulomatous inflammation of respiratory tract and eosinophilia in patients with preexisting asthma and allergic rhinitis
  - Incomplete presentations may also occur

## ETIOLOGY/PATHOGENESIS

### Poorly Understood

- Most patients (variable percentages depending on study) have p-ANCA antibodies
  - Believed to play role in disease causation
- Some cases related to montelukast (Singulair) ingestion

## CLINICAL ISSUES

### Epidemiology

- Age
  - Can present at wide variety of ages, but 3rd and 4th decades are most common
  - Rare onset in childhood
- Sex
  - Slightly more common in men

### Presentation

- Necrotizing vasculitis and asthma almost always present
  - Can occur simultaneously, but asthma typically precedes vasculitic lesions
- Although upper respiratory tract and pulmonary involvement is most common, cutaneous lesions can be seen in 40-70% of patients
- Cutaneous lesions can vary from distinctive nodules, papules, vesicles, petechiae, erythema, or ulceration

### Treatment

- Drugs
  - Cyclophosphamide alone or with corticosteroids is mainstay of treatment

### Prognosis

- Variable; most patients respond well to corticosteroids

## MICROSCOPIC

### Histologic Features

- 3 main histologic features are usually present
  - Leukocytoclastic vasculitis involving postcapillary venules plus arterioles
    - Eosinophils often present
  - Tissue infiltration with eosinophils
    - Sometimes release of eosinophil granules and increased eosinophilia of collagen are also noted (supposedly due to destruction of eosinophils)

- Extravascular granulomas (Churg-Strauss granulomas) with fibrinoid or eosinophilic central necrosis
  - Eosinophils often interspersed along with neutrophils, histiocytes, lymphocytes, and leukocytoclastic debris
  - Finding is not specific, can be seen in granulomatosis with polyangiitis (GPA) or rheumatoid arthritis, but central inflammatory cells are typically neutrophils
- Larger arteries of dermis or subcutaneous fat may be affected, simulating polyarteritis nodosa
  - Inflammation of arterioles and small arteries is typically seen in extracutaneous lesions of CSS
    - Cutaneous lesions of CSS presenting with livedo reticularis &/or subcutaneous nodules often show subcutaneous granulomatous arteritis
- Epidermal ischemic necrosis may also be seen

## ANCILLARY TESTS

### Serologic Testing

- Peripheral eosinophilia can be used as marker of disease severity
- Patients are frequently positive for p-ANCA and more rarely positive for c-ANCA
  - Neither correlate with disease activity
    - However, some believe absence of ANCA in patients may indicate disease remission

## DIFFERENTIAL DIAGNOSIS

### Leukocytoclastic Vasculitis

- Not single entity, but histologic pattern that can be seen in various disease processes including CSS (found in almost 1/2 of cases in 1 study)
- Other causes should not have typical extravascular granulomas
- Eosinophils typically not as numerous

### Polyarteritis Nodosa

- Typically no necrotizing extravascular granulomas
- Neutrophils are predominant inflammatory cells (vs. eosinophils in CSS)
- Typically affects medium-sized to small arteries

### Granulomatosis With Polyangiitis

- Marked peripheral eosinophilia is uncommon
- Patients present with ulcerative lesions of upper respiratory tract and hemoptysis (vs. asthma in CSS)
- Palisading granulomas more likely to have peripheral multinucleated giant cell and central neutrophils

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- CSS, GPA, and polyarteritis nodosa can all have clinical and histologic overlap
- Histologic findings in CSS are not pathognomonic
- Careful clinical clinicopathologic correlation is recommended to establish correct diagnosis

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1. Ishibashi M et al: Spectrum of cutaneous vasculitis in eosinophilic granulomatosis with polyangiitis (Churg-Strauss): a case series. *Am J Dermatopathol.* 37(3):214-21, 2015

## KEY FACTS

### TERMINOLOGY

- Systemic illness defined by presence of recurrent oral aphthous ulcerations plus any 2 of the following
  - Genital ulcerations, skin lesions [erythema nodosum (EN)-like lesions, pseudofolliculitis, papulopustular lesions, or postadolescent acneiform lesions], eye lesions (retinal vasculitis or anterior or posterior uveitis), or positive pathergy test

### CLINICAL ISSUES

- Very painful, recurrent ulcerations invariably present
- Other cutaneous lesions are common
  - EN-like lesions, acneiform pustules and papules, pyoderma gangrenosum, Sweet syndrome, furuncles, superficial migratory thrombophlebitis, sterile pustules at point of minor skin trauma (pathergy), and others
- Genital ulcers are similar in appearance to oral lesions and occur in ~ 3/4 of patients

### MICROSCOPIC

- Diagnosis is primarily clinical
- Oral and genital lesions often show nonspecific ulceration ± associated LCV or lymphocytic vasculitis
- No histologic findings are pathognomonic; clinicopathologic correlation is crucial in arriving at correct diagnosis
- Main role of biopsy
  - Confirm clinical suspicion of disease

### TOP DIFFERENTIAL DIAGNOSES

- Benign ulcer
  - Benign ulcer or deep excoriation could appear indistinguishable histopathologically
    - Clinicopathologic correlation is key
- Neutrophilic dermatoses
  - Neutrophilic dermatoses such as Sweet syndrome, pyoderma gangrenosum, bowel-associated dermatitis-arthritis syndrome, and idiopathic pustular vasculitis

### Indurated Plaques With Superficial Erosions

**(Left)** These are indurated plaques on the arm with superficial erosions in a patient with genital and oral ulcerations. Biopsy showed leukocytoclastic vasculitis (LCV) and subcorneal neutrophilic pustulosis compatible with Behçet disease. **(Right)** Behçet disease involving the scrotum shows deep dermal vessels as the focus of a dense inflammatory infiltrate associated with vasculitis.

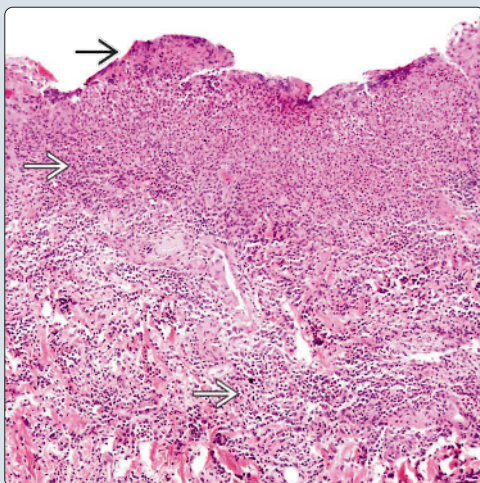


### Deep Dermal Vessels With Vasculitis

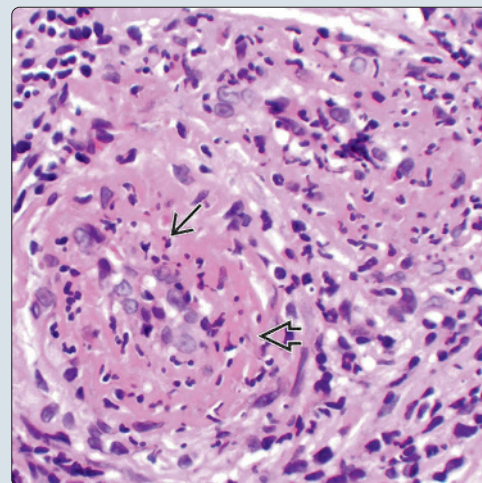


### Ulcer With Dense Dermal Infiltrate

**(Left)** This is a case of Behçet syndrome involving the lip. Note epidermal ulceration and dense dermal inflammatory infiltrate. Although nonspecific, in the proper clinical context, this is consistent with a Behçet ulcer. (Courtesy R. Harris, MD.) **(Right)** A higher power view of Behçet disease involving the scrotum shows LCV of deep dermal vessels with fibrinoid necrosis and karyorrhexis.



### Leukocytoclastic Vasculitis of Deep Dermal Vessels



**TERMINOLOGY****Abbreviations**

- Behçet disease (BD)

**Synonyms**

- Behçet syndrome, oculo-oral-genital syndrome, aphthosis

**Definitions**

- Systemic illness defined by presence of recurrent oral aphthous ulcerations plus any 2 of the following
  - Genital ulcerations, skin lesions [erythema nodosum (EN)-like lesions, pseudofolliculitis, papulopustular lesions, or postadolescent acneiform lesions], eye lesions (retinal vasculitis or anterior or posterior uveitis), or positive pathergy test
  - Oral aphthous ulcers must recur at least 3x over 12-month period

**CLINICAL ISSUES****Epidemiology**

- Age
  - Young adults
  - Peak incidence in 3rd decade
- Sex
  - Male predominance
- Ethnicity
  - Worldwide distribution but highest incidence in Pacific Rim and Mediterranean countries

**Presentation**

- Very painful, recurrent ulcerations invariably present
- Other cutaneous lesions are common
  - EN-like lesions, acneiform pustules and papules, pyoderma gangrenosum, Sweet syndrome, furuncles, superficial migratory thrombophlebitis, sterile pustules at point of minor skin trauma (pathergy), and others
- Genital ulcers are similar in appearance to oral lesions and occur in ~ 3/4 of patients
- Extracutaneous manifestations categorized as oral/genital aphthae, vascular, ocular, intestinal, neural, respiratory, renal, or arthritic
- Vascular Behçet disease
  - Vasculitis can affect any artery and may cause deadly aneurysms
  - Thrombophlebitis is common and affects superficial and deep veins
  - Occlusive main vessel thromboses may also occur (especially involving superior vena cava)
- Ocular Behçet disease
  - If left untreated, blindness will occur secondary to optic atrophy, glaucoma, or cataracts
  - Can involve any part of ocular system
  - Includes retinal vasculitis, uveitis, conjunctivitis, hypopyon, corneal ulceration, choroiditis
- Entero-Behçet disease
  - Can include ulcerations, perforation(s), diarrhea, constipation, abdominal pain, and vomiting
- Neuro-Behçet disease
  - Associated with poor prognosis

- Can affect any part of central or peripheral nervous system and therefore varies greatly, depending on location of lesion
- Oligoarthritis is also not uncommon in patients and may involve wrists, elbows, ankles, and knees
- Renal disease can include proteinuria, hematuria

**Prognosis**

- Mortality estimated at 2-4%

**MICROSCOPIC****Histologic Features**

- Oral and genital lesions often show nonspecific ulceration ± associated leukocytoclastic vasculitis (LCV) or lymphocytic vasculitis
- Can be divided into 3 groups: Vascular, extravascular, and acneiform
- Vascular
  - Early lesions often show lymphocyte-predominant LCV
  - Endothelial swelling that can obliterate lumen
  - Neutrophilic vascular reaction that mimics Sweet syndrome may occur
- Extravascular
  - Dermal lymphocytic or neutrophil-predominant inflammation can occur along with panniculitis, ± associated vascular changes
  - Panniculitis can be septal or lobular
  - Diffuse dermal neutrophilic inflammation can occur ± abscess formation
- Acneiform
  - Suppurative or mixed granulomatous folliculitis
  - Subcorneal pustules may develop

**DIFFERENTIAL DIAGNOSIS****Benign Ulcer**

- Benign ulcer or deep excoriation could appear indistinguishable histopathologically
  - Clinicopathologic correlation is key
- Histopathologically, blood vessels beneath benign ulcers or deep excoriations can show vasculitis
  - However, it is secondary to ulcer and not true vasculitis
  - Clinical correlation and concomitant biopsy of nonulcerated skin can help distinguish primary (true vasculitis) from secondary vasculitis

**Neutrophilic Dermatoses**

- Neutrophilic dermatoses such as Sweet syndrome, pyoderma gangrenosum, bowel-associated dermatitis-arthritis syndrome, and idiopathic pustular vasculitis

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1. Kutlubay Z et al: Histopathological and clinical evaluation of papulopustular lesions in Behçet's disease. *Clin Exp Rheumatol*. 33(6 Suppl 94):S101-6, 2015
2. Uva L et al: Mucocutaneous manifestations of Behçet's disease. *Acta Reumatol Port*. 38(2):77-90, 2013
3. Demirkesen C et al: Clinicopathologic evaluation of nodular cutaneous lesions of Behçet syndrome. *Am J Clin Pathol*. 116(3):341-6, 2001
4. Chen KR et al: Cutaneous vasculitis in Behçet's disease: a clinical and histopathologic study of 20 patients. *J Am Acad Dermatol*. 36(5 Pt 1):689-96, 1997
5. Chun SI et al: Histopathologic study of cutaneous lesions in Behçet's syndrome. *J Dermatol*. 17(6):333-41, 1990



## KEY FACTS

### TERMINOLOGY

- Idiopathic, rare thrombotic disorder characterized by distinctive skin lesions, often associated with infarctive lesions of other organs
  - Multisystem (often fatal) and benign purely cutaneous forms

### CLINICAL ISSUES

- Typically affects trunk and proximal extremities
- Can affect GI system in any area (mouth to anus) but typically affects small intestine
- Death is most often due to peritonitis secondary to intestinal perforation(s)
- Untreated patients survive on average only 2 years after disease development

### MICROSCOPIC

- Most characteristic findings in well-developed lesions
  - Epidermal atrophy and overlying hyperkeratosis

- Underlying wedge-shaped dermal infarct
- Marked endothelial swellings of venules
- Mucin initially in ischemic (infarcted) zone but in older lesions may be at margins of infarct
- Biopsies from patients with benign disease or systemic involvement are indistinguishable

### TOP DIFFERENTIAL DIAGNOSES

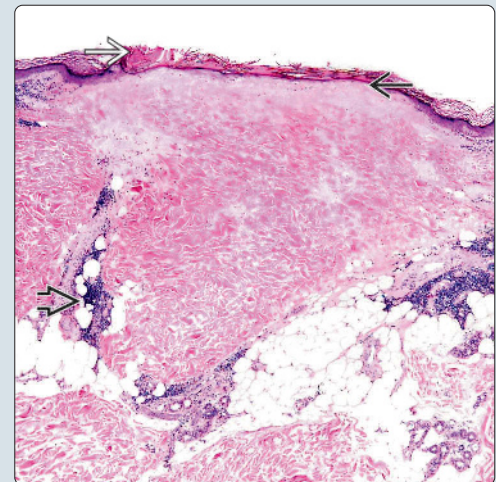
- Autoimmune or collagen vascular disease
  - Similar lesions have been described in systemic lupus erythematosus, dermatomyositis, and systemic sclerosis
- Scar
  - Dermal vessels are unaffected (no fibrin) and typically vertically oriented (in reference to the epidermis)
- Vasculitis
  - Extravasated erythrocytes, leukocytoclasia (nuclear dust), and eosinophils
- Thrombotic vasculopathy
  - Thrombi within vessels

**Porcelain-White Necrotic Ulcers**

(Left) This image shows a porcelain-white, well-demarcated necrotic ulcer on the penis of this patient with Degos disease. (Courtesy PMPH-USA Publishing.) (Right) Characteristic low-power morphology of Degos disease shows a dermal, wedge-shaped infarct with a perivascular lymphocytic infiltrate in adjacent vessels [A], epidermal atrophy [B], and overlying hyperkeratosis [C].

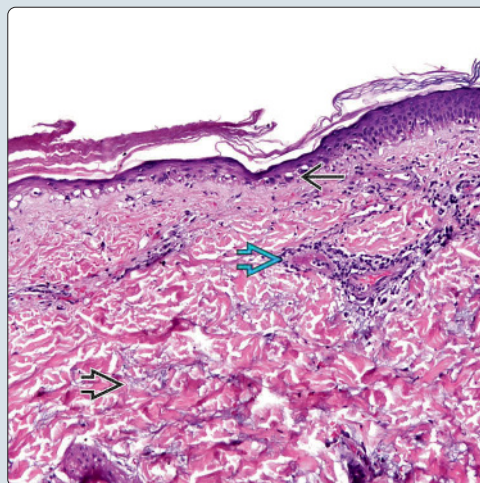


**Wedge-Shaped Infarct**

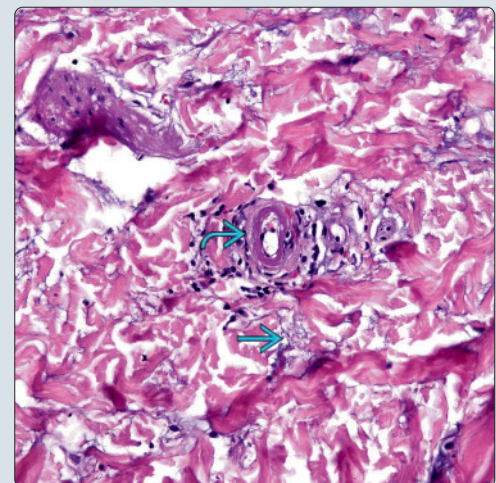


**Epidermal Atrophy and Endothelial Swelling**

(Left) Older lesions of Degos disease show epidermal atrophy [A] with overlying hyperkeratosis. Note the endothelial swellings of venules [B], perivascular lymphocytic infiltrate, and mucin deposition [C]. (Right) High-power view of Degos disease demonstrates interstitial mucin deposition [A] and perivascular fibrin deposition [B] with a mild perivascular lymphocytic infiltrate.



**Interstitial Mucin and Perivascular Fibrin Deposition**



## TERMINOLOGY

### Synonyms

- Malignant atrophic papulosis
- Lethal intestinocutaneous syndrome

### Definitions

- Idiopathic, rare, often fatal multisystem thrombotic disorder characterized by distinctive skin lesions, often associated with infarctive lesions of other organs (especially small bowel)

## ETIOLOGY/PATHOGENESIS

### Unknown

- Some hypothesize it is not distinct entity, but may be reaction pattern to various vascular insults that have not yet been fully determined

## CLINICAL ISSUES

### Epidemiology

- Age
  - Usually affects young and middle aged
    - However, has been described from infancy to 67 years
  - Mean age at presentation: 33 years
- Sex
  - M > F (3:1)

### Site

- Typically affects trunk and proximal extremities
  - Bulbar conjunctiva, buccal, and genital mucosa can also be involved
- Can affect GI system in any area (mouth to anus) but typically affects small intestine
- CNS involvement can occur and other viscera can also develop infarcts

### Presentation

- Begins as crops of pinkish or yellow-gray papules up to 5 mm in diameter, often on trunk and proximal extremities
  - Palms, soles, face, and scalp are typically spared
- Over time, lesions develop into characteristic discrete small patches with central zone of depressed, white, porcelain-like appearance and fine scale
  - Depressed white central zones often surrounded by narrow red or violaceous telangiectatic rim
- Finally, lesions leave atrophic scar
- Divided into purely cutaneous and systemic variant
  - Purely cutaneous or benign Degos disease is typically associated with normal lifespan and only cutaneous lesions
- Gastrointestinal involvement typically occurs in 60% of patients within year of presentation
  - White or yellow depressed plaques can occur from mouth to anus (predominantly small intestine) and can cause infarcts resulting in perforation or fistula formation

### Treatment

- Drugs
  - Eculizumab and Treprostinil to date are the only 2 drugs with proven success

- Often used in combination

### Prognosis

- Untreated patients survive on average only 2 years after disease development
- Death is most often due to peritonitis secondary to intestinal perforation(s)
  - Death can also occur less commonly from cerebral infarcts
- Purely cutaneous variant does not affect longevity

## MICROSCOPIC

### Histologic Features

- Most characteristic findings in well-developed lesions
  - Epidermal atrophy (especially older lesions) commonly with overlying hyperkeratosis
  - Underlying, wedge-shaped, dermal infarct with broad base parallel to surface epithelium
    - Associated mucin deposition that is metachromatic with toluidine blue and positive with hyaluronidase-sensitive Alcian blue staining
    - Mucin initially in ischemic (infarcted) zone but in older lesions may be at margins of infarct
  - There is often marked endothelial swellings of venules and sometimes arterioles with lumen obliteration
    - Vessels adjacent to infarct (often at base and in subcutaneous fat) can show thromboses, perivascular fibrin, or perivascular lymphocytic infiltrate
- Biopsies from patients with benign disease or systemic involvement are indistinguishable

## DIFFERENTIAL DIAGNOSIS

### Autoimmune or Collagen Vascular Disease

- Similar lesions have been described in
  - Systemic lupus erythematosus
  - Dermatomyositis
  - Systemic sclerosis
- Immunologic work-up is important to rule out collagen vascular etiology

### Scar

- Dermal vessels are unaffected (no fibrin) and typically vertically oriented (in reference to the epidermis)
- Late lesions of Degos disease may be indistinguishable histopathologically

### Vasculitis

- Extravasated erythrocytes, leukocytoclasia (nuclear dust), and eosinophils
  - All 3 findings typically absent in Degos disease

### Thrombotic Vasculopathy

- Thrombi within vessels
- Clinically lesions are not as distinct (not porcelain-white), discrete or as small

## SELECTED REFERENCES

1. High WA et al: Is Degos' disease a clinical and histological end point rather than a specific disease? *J Am Acad Dermatol.* 50(6):895-9, 2004
2. Su WP et al: Clinical and histologic findings in Degos' syndrome (malignant atrophic papulosis). *Cutis.* 35(2):131-8, 1985



# Livedo Reticularis

## KEY FACTS

### CLINICAL ISSUES

- Common presentation of many different disorders producing diminished vascular blood flow
- Fixed, lace-like or reticulated reddish blue to purple patches surrounding pale central areas on lower extremities
- Need to biopsy both pale center and livid rings to maximize chances of identifying significant pathology

### MICROSCOPIC

- Primary livedo reticularis (LR) does not produce significant histopathologic changes
- Secondary LR may show
  - Arterial obliteration
  - Red blood cell sludging
  - Perivascular inflammation and endotheliitis
  - Partial or complete occlusion of vessel lumen
  - Fibrosis and shrinkage of vessels (late stage)

### TOP DIFFERENTIAL DIAGNOSES

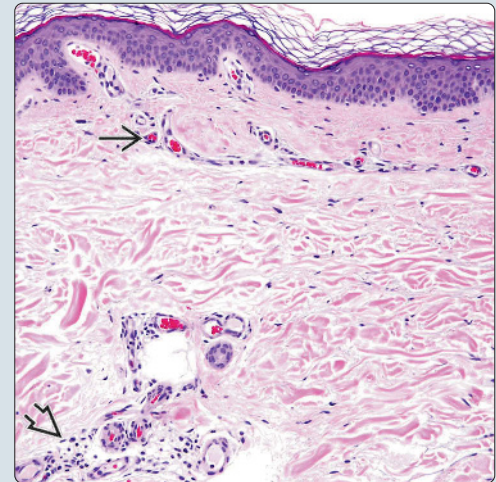
- Other invisible dermatoses
  - Dermatophytosis
    - Careful search for organisms, or PAS stain may reveal fungal organisms
  - Disseminated superficial porokeratosis
    - Cornoid lamellae may be hard to find
  - Cutaneous mastocytosis
    - May see increased numbers of mast cells
  - Pigmentary diseases such as
    - Vitiligo
    - Café au lait spots
    - Ash leaf macules
    - Others

### Net-Like Bands of Purple Discoloration

(Left) Lacey or net-like bands of purple discoloration on the anterior thigh are characteristic of livedo reticularis (LR). Work-up for underlying disease in this patient was negative. (Right) This is a biopsy from idiopathic LR in a patient with Raynaud syndrome. Note minimal changes consisting mainly of vascular dilatation and congestion [E] and a minimal perivascular infiltrate [E].

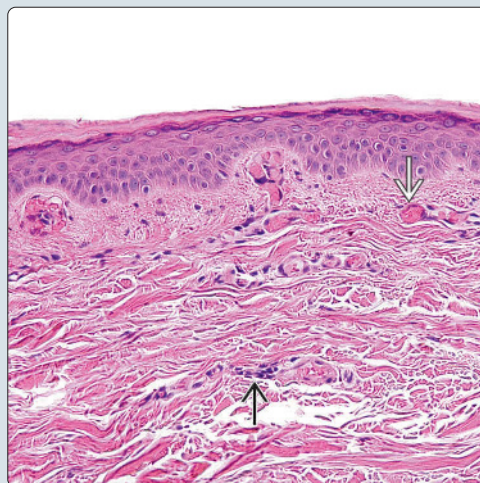


### Vascular Dilatation With Minimal Perivascular Infiltrate

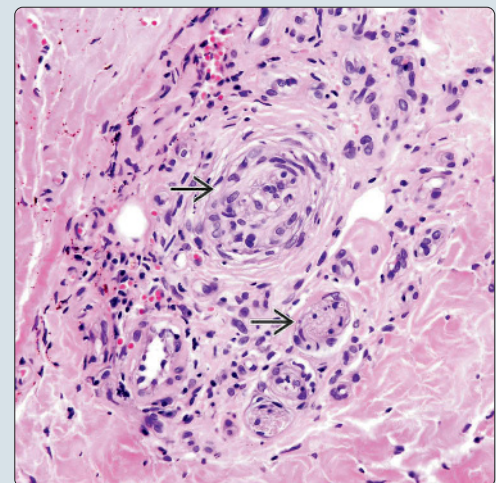


### Red Blood Cell Sludging

(Left) H&E stained section of idiopathic LR demonstrates red blood cell sludging [E] and a mild perivascular infiltrate [E]. (Courtesy S. Florell, MD.) (Right) This is a biopsy from a patient with antiphospholipid syndrome and LR clinically. Note the occlusion of some of the arterioles and a lymphohistiocytic infiltrate [E].



### Occlusion of Vessels in Antiphospholipid Syndrome





## TERMINOLOGY

### Abbreviations

- Livedo reticularis (LR)

### Definitions

- Vascular condition characterized by reddish blue (cyanotic), reticulated (net-like) discoloration of skin, usually involving extremities

## ETIOLOGY/PATHOGENESIS

### Diminished Vascular Perfusion

- Secondary to vasospasm, vasoocclusion, vessel wall injury, or systemically reduced blood flow

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Occurs in about 50% of normal newborn infants and many adults
- Age
  - Depends on form of LR

### Site

- Typically involves lower legs or arms

### Presentation

- Lace-like or reticulated reddish blue to purple patches surrounding pale central areas on lower extremities
- May be transient (usually physiologic and related to cold exposures) or fixed (usually secondary to vasculopathy, vasculitis, or connective tissue disease)

### Treatment

- Idiopathic LR: No treatment necessary
- Secondary LR: Identify and treat underlying condition

### Prognosis

- Usually very good

### Clinical Forms

- Cutis marmorata
  - Develops in ~ 1/2 of normal infants and many adults
  - Occurs following exposure to cold (physiologic response to cold)
  - Disappears upon warming of skin
  - Can be more intense and persistent in debilitated patients
- Cutis marmorata telangiectatica congenita
  - Rare condition that presents with livedo at or soon after birth
  - Can be associated with other congenital problems including
    - Neurological problems
    - Intellectual impairment
  - Can be familial
  - May improve with age
- Idiopathic LR
  - Persistent LR of unknown (idiopathic) cause
  - Affects young women, normally in winter

- May become less prominent but does not resolve with skin warming (vs. physiologic LR)
- Secondary LR
  - Has known cause
  - May be due to autoimmune condition or obstruction of capillaries
  - May be associated with
    - Systemic lupus erythematosus
    - Polyarteritis nodosa
    - Livedo vasculopathy (atrophie blanche)
    - Antiphospholipid antibody syndrome
    - Cholesterol embolism
    - Others including dermatomyositis, rheumatoid arthritis, lymphoma, oxalosis, and cryoglobulinemia
- Sneddon syndrome
  - Very rare syndrome characterized by LR and cerebrovascular lesions
  - Frequently involves trunk, is persistent, and often has more irregular pattern clinically
  - Usually affects young to middle-aged women and may be inherited
  - Often also considered secondary cause of LR

## MICROSCOPIC

### Histologic Features

- May depend on where biopsy was taken (peripheral erythematous areas vs. central whitish area)
  - Some biopsies may only show characteristic changes in just white or erythematous areas
- Multiple punch biopsies are often needed/recommended
  - Can help determine cause of LR
- May have near-normal appearance on biopsy
- Lesional skin may show
  - Arterial obliteration
    - Especially in Sneddon syndrome
  - Red blood cell sludging
  - Perivascular inflammation and endotheliitis (detachment of endothelial cells) initially
  - Partial or complete occlusion of vessel lumen by lymphohistiocytic inflammation and fibrin later
  - Fibrosis and shrinkage of vessels (late stage)
  - May also show vascular dilatation

## DIFFERENTIAL DIAGNOSIS

### Other Invisible Dermatoses

- Dermatophytosis: Careful search for organisms, or PAS stain may reveal fungal organisms
- Disseminated superficial porokeratosis: Cornoid lamellae may be hard to find
- Cutaneous mastocytosis: May see increased numbers of mast cells
- Pigmentary diseases such as vitiligo, café au lait spots, ash leaf macules, others
- Numerous others

## SELECTED REFERENCES

1. Rose AE et al: Livedo reticularis. *Dermatol Online J.* 19(12):20705, 2013
2. In SI et al: The histopathological characteristics of livedo reticularis. *J Cutan Pathol.* 36(12):1275-8, 2009

# Thrombophlebitis

## KEY FACTS

### CLINICAL ISSUES

- Painful, erythematous, cord-like nodules
  - Predominantly affects lower legs
- May arise in varicose veins secondary to prolonged stasis
- Epidemiology
  - Most common in women of child-bearing age
- Occurs in association with
  - Malignancy
  - Behçet disease
  - Thromboangiitis obliterans (Buerger disease)
  - Hypercoagulable states
- Prognosis
  - Usually spontaneously resolves within 2 weeks to 6 months
  - May be associated with deep vein thrombosis and pulmonary embolism

### MICROSCOPIC

- Vasculitis affecting medium-sized veins in subcutis and deep dermis
- Acute thrombophlebitis
  - Dense inflammatory infiltrate with neutrophils
  - Thickened vessel wall
  - Thrombi frequently
- Chronic thrombophlebitis
  - Lymphocytes, histiocytes, and multinucleated giant cells within vein wall
  - Marked thickening of vessel wall
  - Recanalization of thrombus

### TOP DIFFERENTIAL DIAGNOSES

- Arteritis (all types)
- Panniculitis
- Cellulitis
- Deep vein thrombosis
- Sclerosing lymphangitis of penis

### Erythematous Cord-Like Nodules




(Left) Superficial migratory thrombophlebitis classically presents as an erythematous cord-like nodule  on the left medial shin in this patient. (Courtesy J. Steger, MD.) (Right) On low power, thrombophlebitis shows an organized vasculitis with a thick, compact, oval-shaped vessel wall .

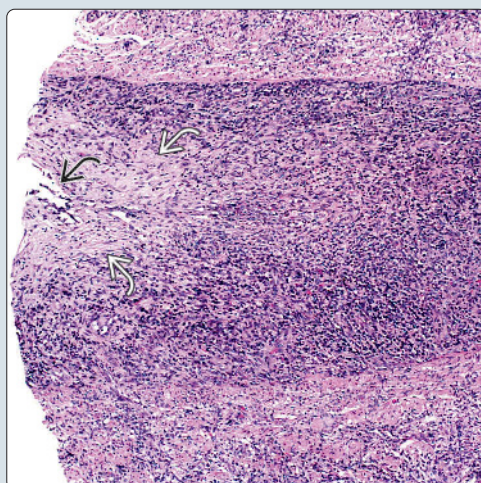


### Organized Vasculitis in Deep Dermis/Subcutis

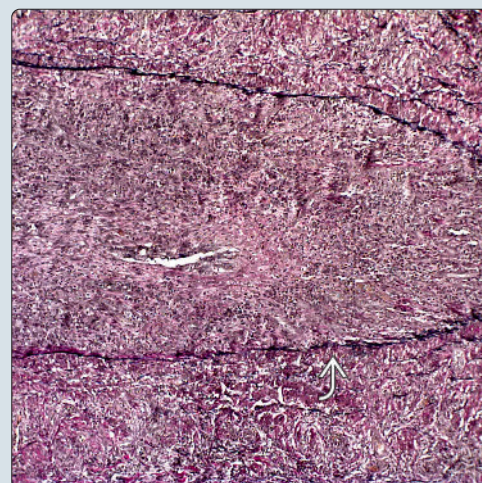


### Inflammatory Infiltrate With Occlusion

(Left) Thrombophlebitis shows an intense mixed inflammatory infiltrate within a fibrotic occlusion  of the vein. There is recanalization  through the fibrotic intima. (Right) Elastic van Gieson stain shows staining of the elastic fibers in the muscular layer .



### Elastic Stain



## TERMINOLOGY

### Abbreviations

- Superficial thrombophlebitis (STP)

### Definitions

- Vasculitis and occlusion of medium-sized veins of upper subcutis or deep dermis

## CLINICAL ISSUES

### Epidemiology

- Sex
  - Most common in women of child-bearing age

### Presentation

- Painful, erythematous, cord-like nodules
  - Predominantly affects lower legs
- May arise in varicose veins secondary to prolonged stasis
- Occurs in association with
  - Malignancy
  - Behçet disease
  - Thromboangiitis obliterans (Buerger disease)
  - Hypercoagulable states

### Treatment

- Surgical approaches
  - Saphenofemoral ligation with stripping of long saphenous vein
  - Phlebectomies
  - Varicose vein removal
- Drugs
  - NSAIDs for symptom palliation
- Others
  - Sclerotherapy
  - Radiofrequency and laser ablation

### Prognosis

- Usually spontaneously resolves within 2 weeks to 6 months
- May be associated with deep vein thrombosis and pulmonary embolism

### Variants

- Trousseau syndrome
  - "Migratory" thrombophlebitis associated with internal malignancy
    - Not actually migratory but discontinuous involvement along single vein
- Mondor disease
  - Thrombophlebitis of chest or breast associated with trauma, surgery, or herpes zoster

## IMAGING

### Ultrasonographic Findings

- Noncompressible tubular structure
  - Hypoechoic and irregular
  - Located in deep dermis or subcutaneous tissue
  - No blood flow

## MICROSCOPIC

### Histologic Features

- Vasculitis affecting medium-sized veins in subcutis and deep dermis
  - Acute thrombophlebitis
    - Dense inflammatory infiltrate with neutrophils
    - Thickened vessel wall
    - Thrombi frequently
    - Intramural microabscesses in Buerger disease
  - Chronic thrombophlebitis
    - Lymphocytes, histiocytes, and multinucleated giant cells within vein wall
    - Marked thickening of vessel wall
    - Recanalization of thrombus
- Assessment of smooth muscle pattern can identify artery from vein
  - Artery: Continuous muscle fibers
  - Vein: Muscle with interspersed collagen
- Infectious organisms should be absent

## ANCILLARY TESTS

### Histochemistry

- Elastic van Gieson
  - Will stain internal elastic lamina

## DIFFERENTIAL DIAGNOSIS

### Arteritis (All Types)

- Affects arteries, not veins
  - Elastic stain can identify internal elastic lamina
  - Smooth muscle pattern can help confirm arterial origin

### Panniculitis

- Vasculitis may be present
- Lobular, septal, or septolobular pattern of infiltration
- Fat necrosis
- Different clinical presentation

### Cellulitis

- Painful erythematous patches
- Due to infection
  - Not of vascular origin
  - Involvement of vessels secondary to inflammation

### Deep Vein Thrombosis

- Occurs in large veins
- Usually too deep to have cutaneous manifestations
- Ultrasound is needed to confirm diagnosis

### Sclerosing Lymphangitis of Penis

- Cord-like nodule of dorsal penis
- Fibrin thrombus or eosinophilic material in lumen
- May be lymphatic or venous

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# Pernio

## KEY FACTS

### TERMINOLOGY

- Synonyms: Chilblains, perniosis
- Pernio may occur in setting of systemic lupus erythematosus
  - In that setting, proper term is chilblains lupus erythematosus
  - Lupus pernio is manifestation of sarcoidosis and has no relation to pernio/chilblains

### ETIOLOGY/PATHOGENESIS

- Caused by exposure to cold, damp conditions, especially in unacclimatized individual
- May be associated with connective tissue diseases, most commonly lupus erythematosus
- Rare familial cases caused by mutation in *TREX1* gene

### CLINICAL ISSUES

- Tender erythematous or violaceous papules occur following cold exposure

- Predominantly seen on acral skin, ears, and nose
- Tend to spontaneously regress after 2-3 weeks

### MICROSCOPIC

- Superficial and deep perivascular infiltrate of lymphocytes
- Prominent perieccrine inflammatory infiltrates
- Papillary dermal edema, with lymphocytes and erythrocytes in papillary dermis
- May see epidermal change (vacuolar alteration, keratinocyte necrosis)

### TOP DIFFERENTIAL DIAGNOSES

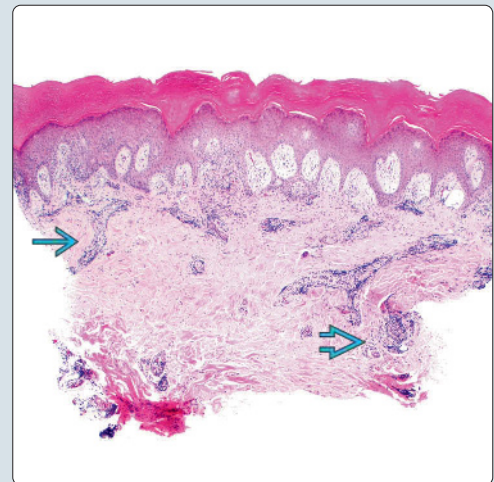
- Polymorphous light eruption: Nonacral skin, mixed infiltrate
- Erythema multiforme: Prominent interface and dyskeratosis
- Tumid lupus erythematosus: Nonacral skin, increased interstitial mucin

**Necrotic Areas Over Toes**

(Left) *Pernio* shows vasculitic necrotic areas over the toes on cold exposure. The patient also suffered from Raynaud. (Right) On scanning magnification, a superficial and deep perivascular and periadnexal infiltrate is seen. The acral location can be inferred by the thick cornified layer, presence of a stratum lucidum, and lack of hair follicles.

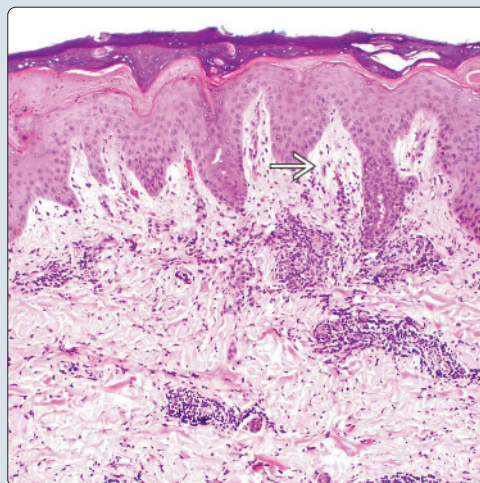


**Scanning Magnification of Pernio**

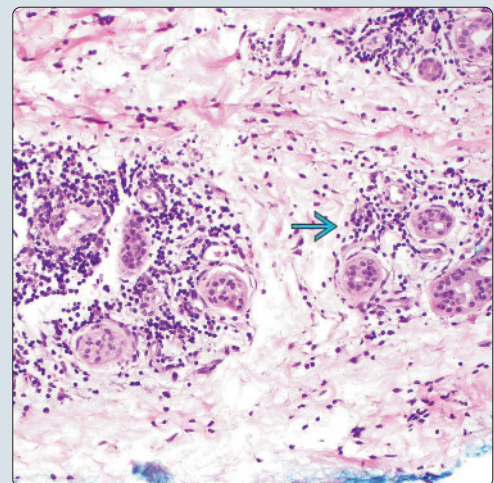


**Papillary Dermal Edema**

(Left) A superficial and deep perivascular and periadnexal infiltrate of lymphocytes is seen on acral skin. Papillary dermal edema and pallor is also typical of perniosis. (Right) In the deep dermis, there are nodular perivascular and periadnexal infiltrates of lymphocytes. Involvement of the eccrine glands is especially typical of perniosis.



**Perieccrine Inflammation**



## TERMINOLOGY

### Synonyms

- Perniosis, chilblains

### Definitions

- Cold-induced inflammatory lesions, predominantly on acral skin

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- Induced by exposure to cold, damp conditions
- Usually seen in winter, but may occur in warmer climates in patients exposed to cold from refrigeration devices or ice
- More common in patients who are not habitually adapted to cold weather

### Genetic Predisposition

- Familial cases of pernio are linked to mutations in *TREX1* gene
- May be seen as part of Aicardi-Goutieres syndrome in pediatric population

## CLINICAL ISSUES

### Epidemiology

- May be idiopathic or occur in association with other conditions
- Most common association is with systemic lupus erythematosus (chilblains lupus erythematosus)
- May be associated with other connective tissue disease or rarely lymphoproliferative diseases

### Presentation

- Patients present with acute onset of single or multiple erythematous to violaceous papules or nodules
- Patients may experience burning or pain
- Lesions predominate on digits and acral surfaces
  - Toes are most common site of involvement
- May also affect ears and nose, rare on trunk

### Treatment

- Adjuvant therapy
  - Warming of extremities and avoidance of cold is mainstay of treatment
  - Smoking cessation
  - Avoid tight fitting or restrictive clothing
- Drugs
  - May treat medically with calcium channel blockers

### Prognosis

- Lesions tend to spontaneously resolve in 2-3 weeks

## MICROSCOPIC

### Histologic Features

- Acral skin: Thick, compact cornified layer, stratum lucidum, numerous eccrine glands, lack of hair follicles
- Most common pattern is superficial and deep perivascular and periadnexal infiltrate of lymphocytes
- Papillary dermal edema with pallor and expansion of dermal papillae

- May also see inflammatory cells (lymphocytes) and extravasated erythrocytes in dermal papillae
- Perieccrine infiltrates, especially in idiopathic pernio
- Perieccrine mucin deposition
- May see epidermal changes
  - Vacuolar alteration of basement membrane, especially in cases associated with lupus
  - Rare individually necrotic keratinocytes

## ANCILLARY TESTS

### Serologic Testing

- May show evidence of cold agglutinins, cryoglobulins
- May see evidence of associated connective tissue disease (antinuclear antibodies, rheumatoid factor)

## DIFFERENTIAL DIAGNOSIS

### Erythema Multiforme

- Vacuolar interface dermatitis with dyskeratosis
- Usually lacks deep inflammation

### Polymorphous Light Eruption

- Shares finding of superficial and deep perivascular and periadnexal inflammation
- Usually has admixed neutrophils or eosinophils
- Predominates on nonacral skin
- Usually lacks perieccrine accentuation

### Tumid Lupus Erythematosus

- Superficial and deep perivascular and periadnexal infiltrates
- Does not occur on acral skin
- Has marked increase in interstitial mucin

### Reticular Erythematous Mucinosi

- Resembles tumid lupus erythematosus
- Lacks acral involvement
- Has marked increase in interstitial mucin

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Lesions predominate on acral skin

### Pathologic Interpretation Pearls

- Papillary dermal edema
- Superficial and deep infiltrate of lymphocytes
- Prominent perieccrine involvement

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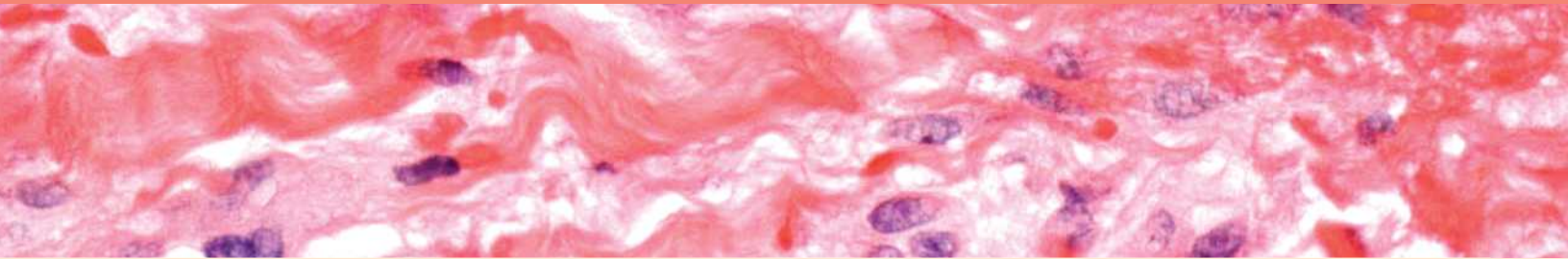
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## SECTION 5

# Panniculitides



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# Erythema Nodosum

## KEY FACTS

### TERMINOLOGY

- Erythema nodosum (EN)

### ETIOLOGY/PATHOGENESIS

- Associated with numerous bacterial, fungal, protozoal, and viral infectious agents as well as numerous medications

### CLINICAL ISSUES

- Represents clinical syndrome, with complex symptoms and signs with multiple, different etiologies

### MICROSCOPIC

- Histologic features
  - All histologic changes are present in and adjacent to septa of subcutaneous tissue, with minimal superficial and deep dermal perivascular lymphocytic inflammation
  - **Early lesions**
    - Edematous septa with prominent mixed cell inflammatory infiltrate, most intense at septa periphery

### ◦ Late lesions

- Widening of septa with fibrosis and macrophage-rich inflammation, with phagocytosed lipid from damaged adipocytes (foam cell)

### TOP DIFFERENTIAL DIAGNOSES

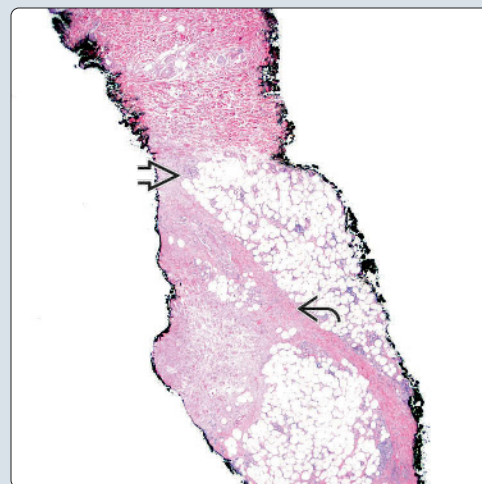
- Different diseases should be considered in differential diagnosis of each stage
- **Early EN**
  - $\alpha$ -1-antitrypsin-associated panniculitis
  - Behçet disease
  - Nodular vasculitis
  - Cutaneous polyarteritis nodosum
- **Late EN**
  - Stasis-associated sclerosing panniculitis
  - Sclerosing panniculitis
  - Nephrogenic systemic fibrosis

**Tender Erythematous Nodule**

(Left) Erythema nodosum (EN) presented as a tender erythematous plaque over the pretibial area in a man with an extensive work-up that was unable to find an underlying cause. Biopsy was confirmatory. (Right) A late lesion of EN shows fibrosis involving the septa of the deep subcutis and extending into adjacent lobules.

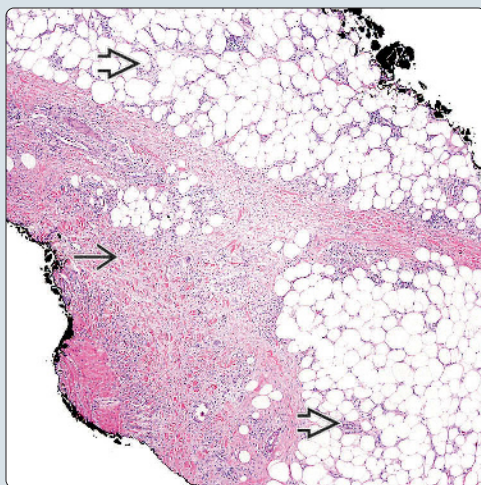


**Septal Panniculitis**

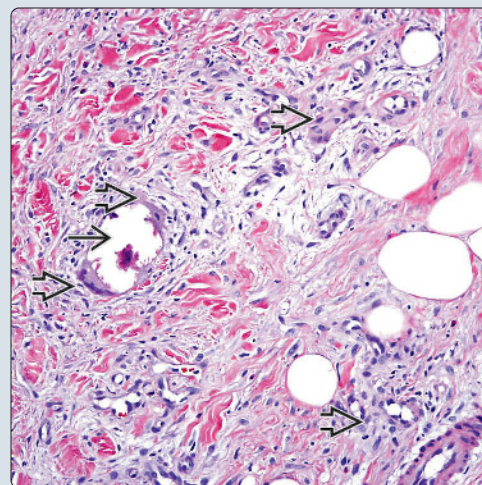


**Thickening of Septa**

(Left) Image shows erythema nodosum, late lesion, at 40x. Fibrosis and thickening of septa with granulomas, mixed inflammation, and lobular involvement. Vascular involvement is absent. (Right) A late lesion of EN demonstrates a Miescher radial granuloma. Aggregations of small histiocytes around a central cleft are characteristic of a Miescher granuloma.



**Miescher Radial Granuloma**



## TERMINOLOGY

### Abbreviations

- Erythema nodosum (EN)

### Synonyms

- Erythema nodosum migrans (chronic form)
- Subacute nodular migratory panniculitis of Villanova and Piñol (chronic form)

### Definitions

- Most common nodular panniculitis with tender, bilateral, symmetric nodules, usually affecting anterior lower extremities of young and middle-aged adults
- Final common pathway of many insults and is thought to be hypersensitivity reaction centered in subcutis
- Prototype of septal panniculitis

## ETIOLOGY/PATHOGENESIS

### Etiology Remains Unclear

- EN is associated with numerous bacterial, fungal, protozoal, and viral infectious agents
  - Streptococcal infection is most common culprit in children
- Associated with many medications
  - Most commonly sulfonamides, but also
    - Estrogens
    - Oral contraceptives
  - May possibly be type IV delayed hypersensitivity reaction
  - Erythema nodosum migrans is specifically related to
    - Pregnancy
    - Oral contraceptives
    - Streptococcal infection
    - Thyroid disease
- Predilection for dependent body parts suggests that trauma or decreased blood flow may play role in localization of lesions

## CLINICAL ISSUES

### Epidemiology

- Age
  - Most often in young and middle-aged adults
- Sex
  - Both acute and chronic forms of EN have predilection for females

### Site

- **Acute erythema nodosum**
  - Has strong predilection for anterior and lateral surfaces of lower extremities
  - May also occur on calves and thighs (moderate disease) and forearms, hands, and face (severe disease)
- **Chronic erythema nodosum**
  - Lesions are typically distributed unilaterally on lower extremity

### Presentation

- **Acute erythema nodosum**
  - Presents suddenly, with painful, warm, erythematous subcutaneous nodules or plaques

- Lesions later become bluish purple and then yellow, reminiscent of bruise
- Lesions are typically distributed symmetrically and have average diameter of 1-5 cm
- Lesions involute spontaneously without residual scar
- Other systemic symptoms may be present, such as fever, malaise, leukocytosis, and arthropathy

- **Chronic erythema nodosum/subacute nodular migratory panniculitis**

- Somewhat controversial entity
- Up to several red, subcutaneous, nontender nodules distributed asymmetrically
- Nodules enlarge and develop into plaques, often with central clearing
- May persist for several months up to several years

### Treatment

- Acute EN
  - Nonsteroidal antiinflammatory drugs, corticosteroids, and potassium iodide
  - Corticosteroids
  - Potassium iodide
- Chronic EN
  - Infliximab and adalimumab have been successful

## MICROSCOPIC

### Histologic Features

- All histologic changes are present in and adjacent to septa of subcutaneous tissue, with minimal superficial and deep dermal perivascular lymphocytic inflammation
- **Acute erythema nodosum**
  - **Early lesions**
    - Edematous septa with prominent mixed cell inflammatory infiltrate, most intense at septa periphery
    - Inflammation may extend into fat lobules in lace-like fashion
    - Miescher radial granulomas: Aggregates of macrophages and neutrophils around small blood vessels or cleft-like spaces (also reported in Sweet syndrome, nodular vasculitis, and necrobiosis lipoidica)
    - Fibrin deposition, neutrophilic clusters, red blood cell extravasation, and edematous venular walls with lymphocyte infiltration can be seen
    - Blood vessel wall necrosis and fat necrosis are rare
  - **Late lesions**
    - Widening of septa with fibrosis and macrophage-rich inflammation, with phagocytosed lipid from damaged adipocytes (foam cell)
    - Mixed inflammatory infiltrate, without neutrophils, involves periphery of fat lobules
    - Loosely formed granulomas with multinucleated giant cells are more prominent than in early lesions
    - Latest lesions show maximum fibrosis and minimum inflammation, with lymphocytes and rare eosinophils
    - Vascular changes are minimal and can resolve without scarring
- **Chronic erythema nodosum**
  - Similar to late lesions of acute EN
  - **Erythema nodosum migrans**
    - Densely scarred and thickened septa



- Numerous, large granulomas with epithelioid macrophages and lipogranulomas are more prominent
- Multinucleated giant cells often palisade along septal borders
- Vascular proliferation with thickening of endothelium and red blood cell extravasation is common
- Significant vasculitis as well as absent vasculitis have both been reported
- Coagulation and caseating necrosis invariably absent

## ANCILLARY TESTS

### Electron Microscopy

- Demonstrates damaged endothelial cells of small vessels with extension of inflammatory cells into vessel walls

### Direct Immunofluorescence

- May show immunoglobulin and complement deposition in blood vessel walls

### Laboratory Findings

- Increased erythrocyte sedimentation rate (ESR), leukocytosis, and mild anemia

## DIFFERENTIAL DIAGNOSIS

### Chronological Stage of EN

- Different diseases should be considered each stage

### Histopathologic

- **Early EN**
  - $\alpha$ -1-antitrypsin-associated panniculitis
    - Mostly neutrophilic, involves septa collagen, and spares adipocytes (floating lobule pattern)
  - Behçet disease
    - Has neutrophilic and lymphocytic vasculitis that is predominantly lobular in distribution
  - Nodular vasculitis
    - In contrast to EN, coagulation and caseation-like necrosis are prominent
  - Cutaneous polyarteritis nodosum
    - Necrotizing vasculitis of medium-sized arteries is key finding
- **Late EN**
  - Stasis-associated sclerosing panniculitis
    - Stasis changes with sclerosis that are not seen in EN
  - Sclerosing panniculitis
    - More sclerotic changes than in EN
  - Nephrogenic systemic fibrosis
    - Mild septal mononuclear cell infiltrate and granulomatous inflammation
    - Clinical situation is different than in EN and diffuse fibrosis is present

### Clinical

- **Early EN**
  - Erythema induratum
    - In contrast to EN, these appear on posterior aspects of legs (especially calves) of adult women with erythrocytotic circulation, and are often chronic and ulcerate
    - May be associated with tuberculosis

- Rare
- Erythema induratum of Bazin
  - Regress and leave atrophic scar
- Vasculitis
  - Often petechial
  - Often with livedo reticularis
  - Often on additional sites other than just lower extremities
- Sarcoidosis
  - Patients with acute EN may have hilar lymphadenopathy
  - Biopsy will exclude diagnosis
- Leukocytoclastic vasculitis
  - Distinguished by multiple petechial lesions on lower extremities
- **Chronic EN and late acute EN**
  - Sarcoidosis
    - Granulomatous involvement predominantly of lobules rather than septa
    - Lack of septal fibrosis and thickening
  - Dermatofibroma
    - Less numerous
    - Reddish brown
    - Bound down and indent when pressured from side
  - Deep fungal infection
    - Less numerous
    - Not limited to lower extremities
    - More common in immunosuppressed
  - Prurigo nodularis
    - Very pruritic
    - Excoriation or crusting over surface
  - Subcutaneous lymphoma
    - Biopsy easily differentiates
  - Metastatic carcinoma
    - Biopsy easily differentiates

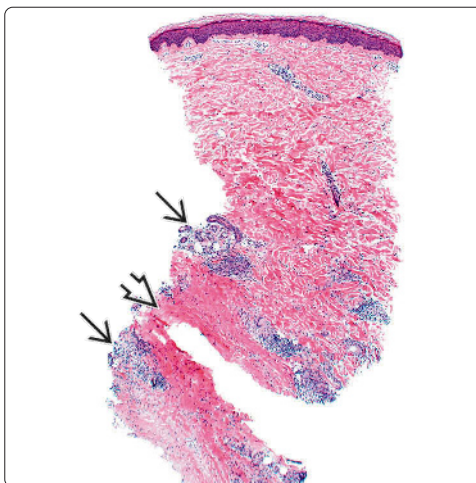
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Close-Up of Erythema Nodosum Nodule

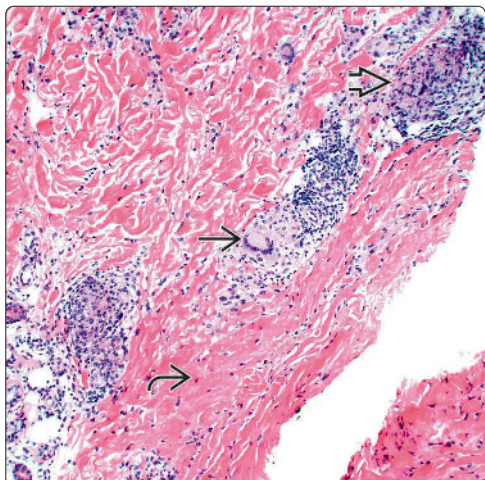


Septal Inflammation

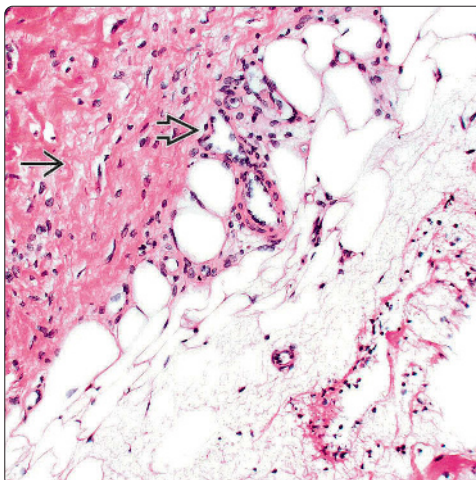


(Left) Erythematous plaque over the pretibial area was diagnostic of EN on biopsy. (Right) EN shows a predominantly septal panniculitis with thickened connective tissue septa, mixed cell inflammation, and focal involvement of lobules. (Courtesy D. Cassarino, MD, PhD.)

Widened Septa

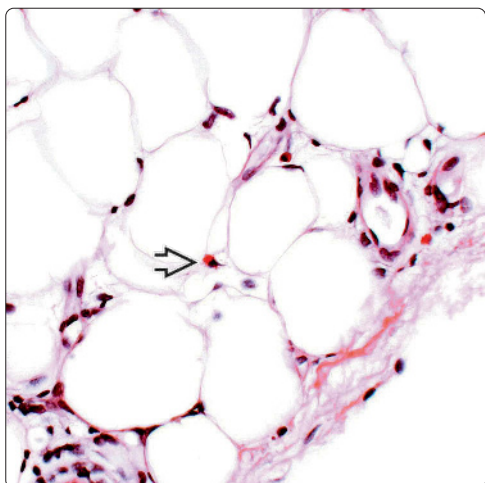


Inflammation Extending Into Lobule

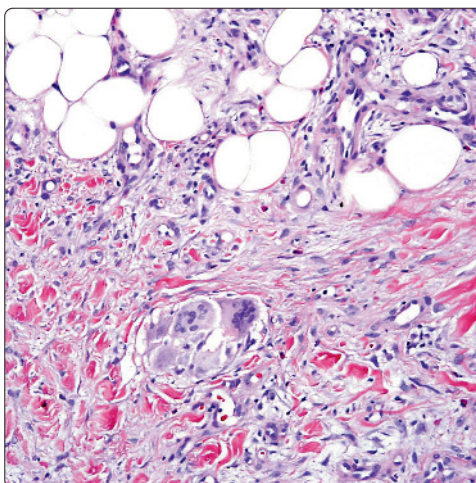


(Left) Early lesions of EN show thickened septa with mixed cell inflammation composed primarily of neutrophils, multinucleate giant cells, and granulomas. (Right) Early lesion of EN shows thickened septa and septal inflammation extending to the periphery of adjacent lobule, with lymphocyte rimming of adipocytes. Minimal fibroplasia is evident in this early lesion. (Courtesy D. Cassarino, MD, PhD.)

Early Lesion



Older Lesion



(Left) Early stage EN shows mild lobular inflammation including rare neutrophils and eosinophils. (Right) Histiocyte-rich inflammatory infiltrate in an older lesion is seen here.



## KEY FACTS

### TERMINOLOGY

- Sclerosing panniculitis, membranous lipodystrophy, sclerodermiform hypodermatitis

### CLINICAL ISSUES

- Acute phase: Extremely painful, violaceous plaques in lower legs
- Chronic phase: Hyperpigmented induration with contracted skin

### MICROSCOPIC

- Early lesion: Nonspecific showing septal and lobular panniculitis
- Membranocystic fat necrosis showing eosinophilic material (PAS positive) in arabesque pattern
  - Sometimes in fractal-like feathery shape
- Cysts of fat showing eosinophilic material (PAS positive) in arabesque pattern

### TOP DIFFERENTIAL DIAGNOSES

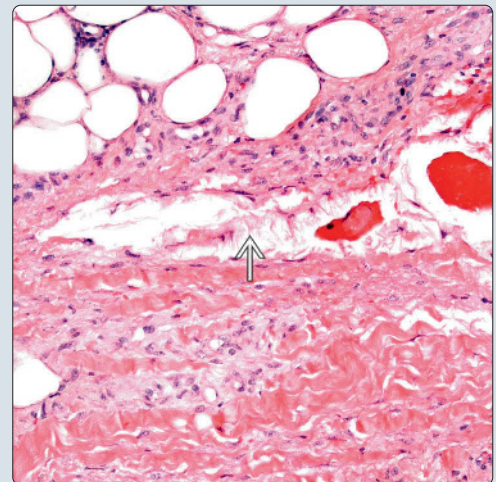
- Cellulitis
  - Mixed inflammation containing neutrophils and eosinophils
- Subcutaneous fat necrosis of newborn
  - Needle-shaped clefts in adipocytes and in multinucleated giant cells
- Factitial panniculitis
  - Different sizes of cystic spaces in subcutis (Swiss cheese pattern)
  - Mixed inflammation
- Morphea
  - Dense dermal sclerosis
- Erythema Nodosum
  - Lymphocytes with histiocytes and multinucleated giant cells, sometimes forming Miescher radial granuloma

(Left) End-stage lipodermatosclerosis in this patient shows inverted wine bottle deformity and distal, shrunk, indurated lower extremities. (Right) Low-power view of lipodermatosclerosis (LDS) demonstrates distinct eosinophilic material ➡ (feathery or arabesque pattern) in fatty cystic degeneration.

Inverted Wine Bottle Deformity

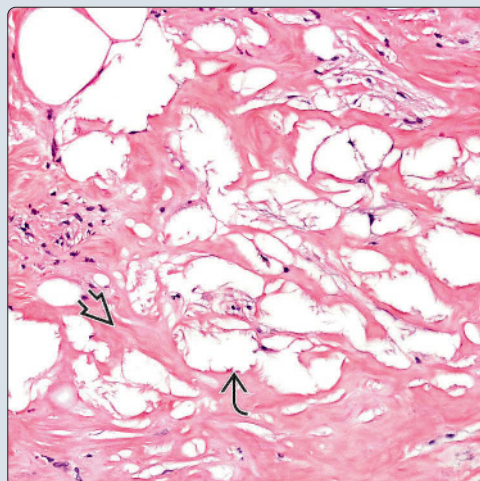


Eosinophilic Material Within Fatty Cystic Degeneration

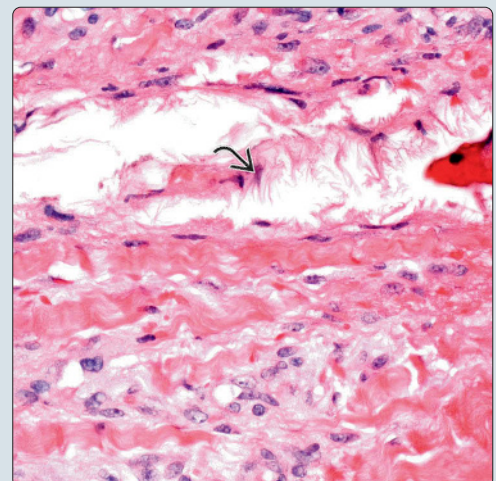


(Left) A later lesion of LDS demonstrates septal fibrosis ➡ with fat degeneration ➡. (Right) Cysts of the fat in LDS show eosinophilic material in an arabesque pattern ➡.

Septal Fibrosis With Fat Degeneration



Arabesque Pattern of Eosinophilic Material





## TERMINOLOGY

### Abbreviations

- Lipodermatosclerosis (LDS)

### Synonyms

- Sclerosing panniculitis, membranous lipodystrophy, sclerodermiform hypodermatitis

### Definitions

- Venous insufficiency leading to skin induration and ulceration

## ETIOLOGY/PATHOGENESIS

### Probably Venous Disease Leading to Skin Ulceration

- Some association with obesity, hypercoagulable state (protein C and S deficiencies)
- Some association with connective tissue disease
- Excessive matrix metalloproteinases (MMP) activity

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Common
- Age
  - Over 40 years old
- Sex
  - Female predominance
- Ethnicity
  - No predilection

### Presentation

- Acute phase: Extremely painful, violaceous plaques in lower legs
- Chronic phase: Hyperpigmented induration with contracted skin
- Ulceration
- CEAP (international consensus committee on chronic venous disease) classification system
  - Class I: No evidence of venous disease
  - Class II: Superficial varicose vein
  - Class III: Varicose veins with edema
  - Class IV: LDS
  - Class V: Venous ulceration

### Treatment

- Drugs
  - Stanozolol (anabolic steroid), intralesional steroids, pentoxifylline, topical capsaicin
- Other options
  - Excision
  - Leg elevation, compression stocking

### Prognosis

- Good; but need to treat underlying disease

## MICROSCOPIC

### Histologic Features

- Early lesion: Nonspecific showing septal and lobular panniculitis

- Membranocystic fat necrosis showing eosinophilic material (PAS positive) in arabesque pattern
  - Sometimes in fractal-like feathery shape
- Microcysts and septal fibrosis

## DIFFERENTIAL DIAGNOSIS

### Cellulitis

- Mixed inflammation containing neutrophils and eosinophils
- Extend into dermis
- Hemorrhages and necrosis
- No eosinophilic material

### Subcutaneous Fat Necrosis of Newborn (Sclerema Neonatorum)

- Needle-shaped clefts in adipocytes and in multinucleated giant cells
- No inflammation in sclerema neonatorum
- Clinically, younger patients

### Factitial Panniculitis

- Different sizes of cystic spaces in subcutis (Swiss cheese pattern)
- Sometimes polarizable materials
- Mixed inflammation

### Morphea

- Dense dermal sclerosis
- Presence of plasma cells in dermis or subcutis
- Loss of adipocytes around adnexal structures
- No eosinophilic material

### Erythema Nodosum

- Predominately septal panniculitis
- Lymphocytes with histiocytes and multinucleated giant cells, sometimes forming Miescher radial granuloma
- Dense widen fibrous septa
- Increase of blood vessels and fibroblast in septa

### Erythema Induratum

- Inflammation extends into fat lobules
- Vasculitis in both arteries and veins
- Inflammation predominately in subcutis
- In erythema induratum, Bazin type, lobular granulomatous panniculitis

### Pancreatic Panniculitis

- Calcification in subcutis, enzymatic fat necrosis, ghost of fat cells
- Neutrophilic infiltrate with nuclear dust
- Fine calcium deposits, no eosinophilic degeneration

### Lupus Panniculitis

- Lobular involvement by many lymphocytes
- Lymphoid follicles with reactive-appearing germinal centers
- Sometimes, epidermal (interface dermatitis) and dermal changes (superficial and deep perivascular and periadnexal inflammation with mucin) seen

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# Traumatic Panniculitis

## KEY FACTS

### TERMINOLOGY

- Localized organizing necrosis of subcutaneous fat resulting from physical or chemical injury

### CLINICAL ISSUES

- Commonly presents as breast mass in young woman who does not remember preceding trauma (often kick from infant or child in arms)
- Warm, indurated, erythematous nodules may occasionally occur, but typically lesion is so deep that no surface change is visible

### MICROSCOPIC




- Early lesions have perivascular inflammatory infiltrate of macrophages and lymphocytes
- More mature lesions demonstrate fat microcysts surrounded by histiocytes
- Eventually, fibrous capsule forms around area of fat necrosis, forming so-called "mobile encapsulated lipoma"

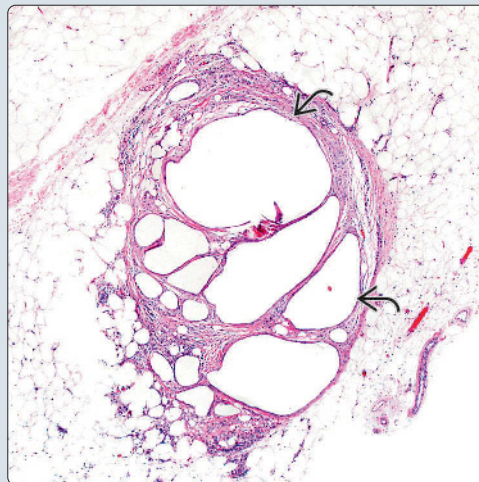
- Late lesions
  - Often demonstrate lipomembranous change, composed of eosinophilic material at periphery of cystic spaces in fern-like pattern resembling frost on window

### TOP DIFFERENTIAL DIAGNOSES

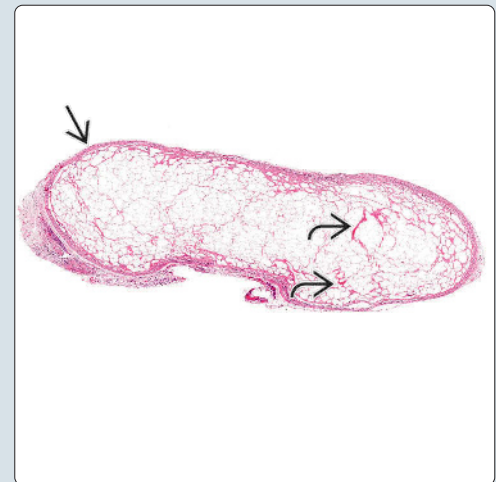
- Cold panniculitis
  - Occurs more often in children, especially on cheeks (popsicle panniculitis)
- Factitial panniculitis
  - Usually secondary to injection of foreign substances into subcutaneous tissue
- Lipoma
  - Histologically, lipocytes are similar in size and shape in contrast to varying sizes of cystic spaces in traumatic panniculitis

#### Cystic Degeneration of Fat Lobules



(Left) Early traumatic fat necrosis is characterized by cystic degeneration of the fat lobule  and a granulomatous response. (Right) Low-power image demonstrates cystic change  within the fat lobule. There is also a suggestion of early fibrous capsule formation .

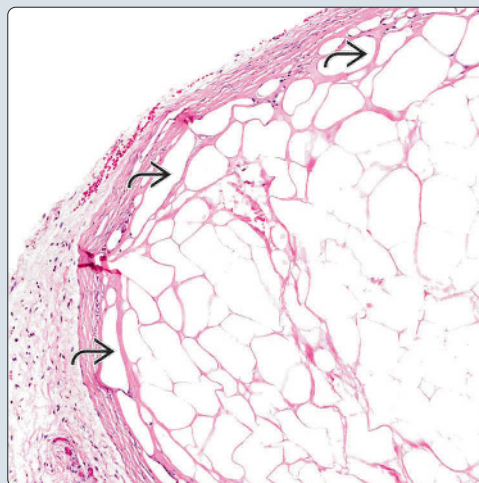


#### Fat Lobule With Cystic Change

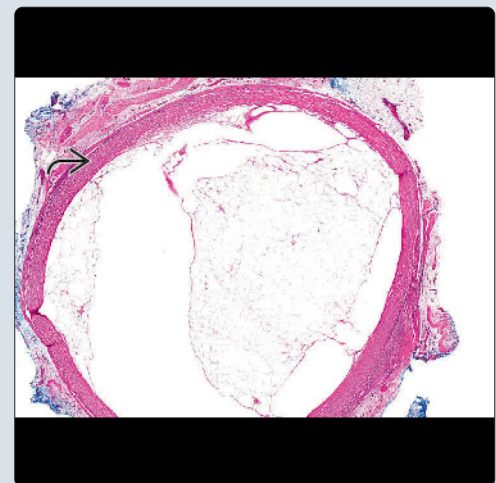


#### Lipomembranous Change

(Left) Medium-power image demonstrates lipomembranous change, composed of eosinophilic material at periphery of cystic spaces . (Right) A fibrous capsule forms  around the area of fat necrosis, forming the so-called "mobile encapsulated lipoma."



#### Fibrous Capsule



## TERMINOLOGY

### Synonyms

- Mobile encapsulated lipoma
- Nodular-cystic fat necrosis

### Definitions

- Localized organizing necrosis of subcutaneous fat resulting from physical or chemical injury

## ETIOLOGY/PATHOGENESIS

### Trauma

- Physical injury from trauma or electricity
- Severity of lesion does not correlate with intensity of inciting trauma

## CLINICAL ISSUES

### Epidemiology

- Age
  - All ages may develop traumatic fat necrosis
  - Commonly presents as breast mass in young women who do not remember preceding trauma (often kick from infant or child in arms)

### Presentation

- Inciting event is typically minor injury of which patient has no recollection
- Variably tender nodule in fatty site, such as breast
- Warm, indurated, erythematous nodules may occasionally occur, but typically lesion is so deep that no surface change is visible

### Treatment

- Diagnostic biopsy removes lesion, curing condition

### Prognosis

- Excellent, although lesions occasionally recur in those prone to repetitive minor injuries

## MICROSCOPIC

### Histologic Features

- Early lesions
  - Perivascular inflammatory infiltrate of macrophages and lymphocytes
- Maturing lesions show rupture of adipocytes, foam cells, and mixture of inflammatory cells (neutrophils, histiocytes, and eosinophils)
- More mature lesions demonstrate fat microcysts surrounded by histiocytes
  - Microcysts characteristically vary in size and shape
  - Foreign body reaction with giant cells, and calcification may be noted
- Eventually, fibrous capsule forms around area of fat necrosis, forming so-called "mobile encapsulated lipoma"
- Late lesions

- Often demonstrate lipomembranous change, composed of eosinophilic material at periphery of cystic spaces in fern-like pattern resembling frost on window

## DIFFERENTIAL DIAGNOSIS

### Cold Panniculitis

- Occurs more often in children, especially on cheeks (popsicle panniculitis)
- Characterized by crystalline rosettes within lipocytes and surrounding granulomatous response

### Factitial Panniculitis

- Usually secondary to injection of foreign substances into subcutaneous tissue
- Lesions are often dramatic in nature, but patient typically demonstrates relative indifference to severity of condition ("La belle indifference")
  - Patient often thrives on attention received
- Histologic sections typically demonstrate mixed suppurative and granulomatous panniculitis, and cultures grow vaginal anaerobes or fecal coliforms

### Lipoma

- Well-circumscribed, nontender tumor composed of mature fat
- Histologically, lipocytes are similar in size and shape in contrast to varying sizes of cystic spaces in traumatic panniculitis

### Angiolipoma

- Well-circumscribed spontaneously painful or tender tumor composed of mature fat and small blood vessels with thrombosis
- Histologically, lipocytes are similar in size and shape in contrast to varying sizes of cystic spaces in traumatic panniculitis
- Characteristic thrombosed vessels are easily visible at scanning magnification

### Spindle Cell Lipoma

- Well-circumscribed, nontender tumor composed of mature fat and septa of fibromyxoid tissue
- Typically large (4-8 cm) and located in subcutaneous tissue of upper back of older individual
- Histologically, myxoid areas are often prominent
- Mast cells are common within these myxoid septa
- Lipocytes are similar in size and shape in contrast to varying sizes of cystic spaces in traumatic panniculitis

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## KEY FACTS

### TERMINOLOGY

- Rare form of panniculitis showing predominantly lobular involvement with many eosinophils
- Not specific disease, but rather reaction pattern

### CLINICAL ISSUES

- Single or multiple skin lesions with localized erythema, dermal papules, &/or localized to diffuse skin and subcutaneous indurations that can ulcerate
- Self-limited condition with excellent prognosis that often resolves upon removal of stimulating antigen

### MICROSCOPIC

- Predominantly lobular panniculitis with many eosinophils, flame figures, some septal involvement, and only minimal fat necrosis or hemorrhage
- Epidermal spongiosis and parakeratosis with variable superficial and deep dermal perivascular infiltrates with eosinophils and lymphocytes

- Flame figures and some septal involvement often seen
- Arthropod assault is frequent cause that may yield epidermal punctum with eosinophils and papillary dermal hemorrhage

### TOP DIFFERENTIAL DIAGNOSES

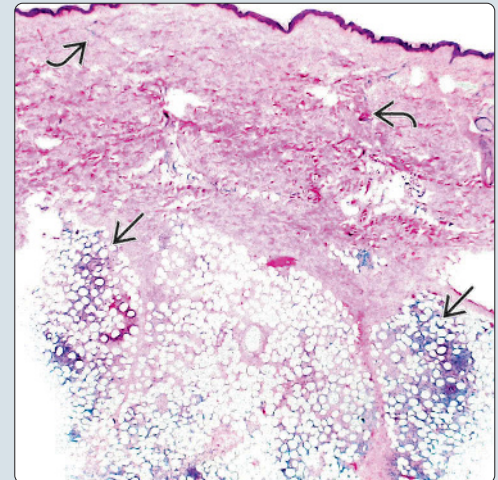
- Eosinophilic panniculitis is histologic pattern with wide differential diagnosis of possible causes
- Hypereosinophilic syndrome
  - Eosinophils, few lymphocytes, no flame figures
- Eosinophilic fasciitis
  - Thick, sclerotic fascia, mixed chronic inflammation with eosinophils involving subcutis
- Wells syndrome
  - Can involve subcutis; early eosinophilic infiltrates without vasculitis; later granulomatous infiltrates
- Arthropod assault
  - Mixed inflammation with eosinophils, lymphocytes, few neutrophils, flame figures

Indurated Nodules

(Left) Eosinophilic panniculitis due to exaggerated hypersensitivity reaction to arthropod bites often manifests as multiple round, well-circumscribed, indurated nodules with overlying erythematous skin. (Right) Eosinophilic panniculitis often shows dermal perivascular inflammation with eosinophils overlying a more impressive predominantly lobular panniculitis that includes some septal involvement and inflammation composed of eosinophils mixed with lymphocytes.

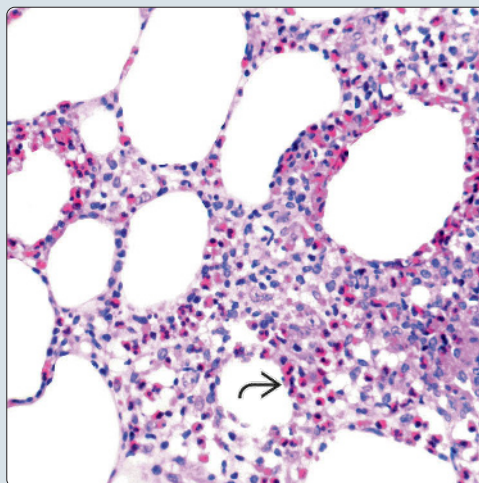


Lobular Panniculitis

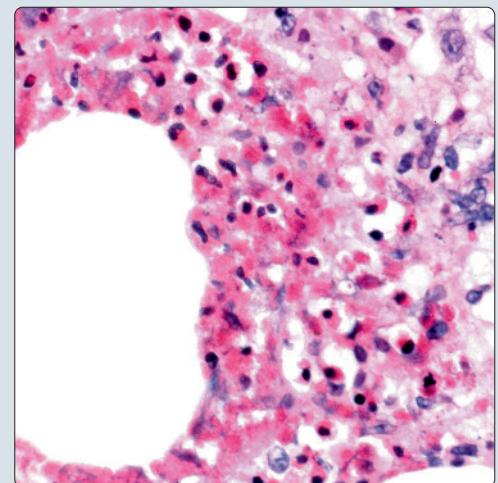


Numerous Eosinophils

(Left) Closer inspection of the lobular inflammation confirms the presence of many eosinophils admixed with lymphocytes. (Right) Foci infiltrated by nearly exclusively eosinophils are seen.



Numerous Eosinophils, High Power



## TERMINOLOGY

### Synonyms

- Lobular eosinophilic panniculitis

### Definitions

- Rare form of panniculitis showing predominantly lobular involvement with many eosinophils, which is not specific disease, but rather nonspecific tissue reaction pattern with associated differential diagnosis

## ETIOLOGY/PATHOGENESIS

### Nonspecific Histopathologic Tissue Reaction

- Predominantly lobular panniculitis with numerous eosinophils can be distinctive histologic pattern, although many conditions rarely produce this pattern
- Seen in clinical hypereosinophilic syndrome, Wells syndrome, erythema nodosum, vasculitis, atopy, eosinophilic fasciitis, trauma, parasitic infections
- Occurs as exaggerated hypersensitivity reaction to drugs and arthropod assaults/spider bites

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Rare
- Age
  - Affects all ages from infancy to elderly
- Sex
  - Both genders affected

### Site

- Any skin site may be involved, but extremities and trunk more commonly

### Presentation

- Nonspecific generalized clinical manifestations are often prominent with drug hypersensitivity reactions and can include fever, pruritus, and malaise
- Single or multiple skin lesions with localized erythema, dermal papules, &/or localized to diffuse skin and subcutaneous indurations that can ulcerate
  - Erythematous skin with dermal papule or circumscribed subcutaneous nodule with central punctum often present when associated with arthropod assault or spider bite
  - Brawny edematous gray plaques to skin and subcutaneous indurations if associated with extension of Wells syndrome into subcutis
  - Severe skin and subcutaneous indurations ± ulceration are common if associated with eosinophilic fasciitis
  - Pruritic red papules or urticarial lesions are distributed on trunk, extremities, and face if associated with hypereosinophilic syndrome
- Also seen with trauma, erythema nodosum, vasculitis, atopy, and parasites

### Laboratory Tests

- CBC to evaluate blood for hypereosinophilia in hypereosinophilic syndrome
- Stool ova and parasites if clinically indicated

### Treatment

- Self-limited condition that often improves with prednisone
- However, best treatment is removal of source of antigenic stimulation when possible

### Prognosis

- Excellent prognosis in most cases

## MACROSCOPIC

### General Features

- Erythema, urticarial lesions, dermal papules, and subcutaneous nodules, plaques, and indurations

## MICROSCOPIC

### Histologic Features

- Epidermal spongiosis and parakeratosis with variable superficial and deep dermal perivascular infiltrates with eosinophils and lymphocytes
- Predominantly lobular panniculitis with inflammation composed of many eosinophils mixed with variable lymphocytes and few neutrophils
- Flame figures and some septal involvement often seen
- Fat necrosis and hemorrhage are minimal to absent
- Arthropod assault is frequent cause that may yield epidermal punctum with eosinophils and papillary dermal hemorrhage
  - Multiple step sections help to see punctum

## DIFFERENTIAL DIAGNOSIS

### Hypereosinophilic Syndrome

- Eosinophils, few lymphocytes, no flame figures

### Eosinophilic Fasciitis

- Thick, sclerotic fascia, mixed chronic inflammation with eosinophils involving subcutis

### Wells Syndrome

- Can involve subcutis; early eosinophilic infiltrates without vasculitis; later granulomatous infiltrates

### Arthropod Assault

- Mixed inflammation with eosinophils, lymphocytes, few neutrophils, flame figures

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Predominantly lobular panniculitis with many eosinophils, flame figures, some septal involvement, and no significant fat necrosis or hemorrhage
- Clinical correlation is essential to identify cause

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## KEY FACTS

### TERMINOLOGY

- Granulomatous lobular panniculitis with vasculitis

### ETIOLOGY/PATHOGENESIS

- Mycobacterium* species, *Brucella* species, hepatitis C

### CLINICAL ISSUES

- Usually multiple painful nodules on calves or shins
- Nodules may coalesce into larger plaques
- Often will resolve with scarring and recur
- Ulceration may occur

### MICROSCOPIC

- Lobular or septolobular panniculitis
- Fat necrosis, fibrosis of septa
- Histiocytes, multinucleated giant cells are numerous
- Granulomas are common
- Remainder of infiltrate may contain neutrophils, lymphocytes, and plasma cells

- Vasculitis of intralobular vessels

### TOP DIFFERENTIAL DIAGNOSES

- Clinical
  - Erythema nodosum
  - Subcutaneous fat necrosis of newborn
  - $\alpha$ -1-antitrypsin deficiency
  - Pancreatic panniculitis
  - Sarcoidosis
  - Lupus panniculitis (a.k.a. lupus profundus)
- Histological
  - Rheumatoid arthritis (neutrophilic lobular panniculitis)
  - Crohn disease
  - Erythema nodosum leprosum
  - Lucio phenomena

(Left) Erythema induratum shows an indurated lower leg with a necrotic nodule. The patient had a positive PPD skin test and responded to anti-TB antibiotics. (Right) Erythema induratum shows an indurated lower leg with a necrotic and crusted nodule. The patient had a positive PPD skin test and responded to anti-TB antibiotics.

Necrotic and Crusted Nodule

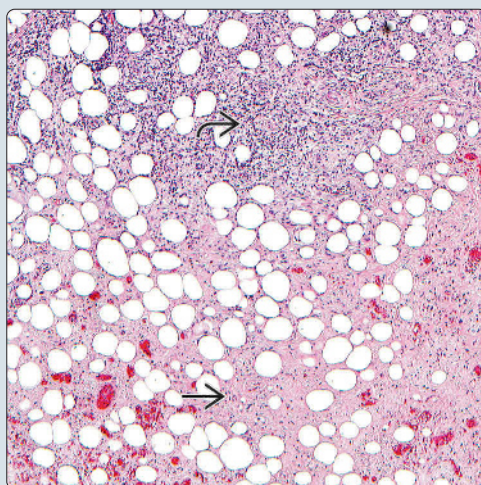


Indurated Background Surrounding Necrotic Nodule

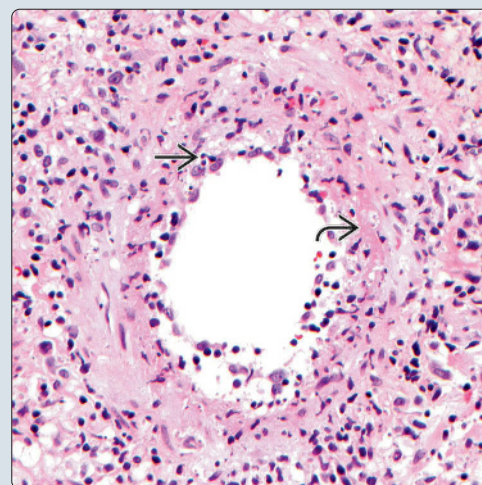


(Left) Erythema induratum is a predominantly lobular panniculitis. Here, there is prominent fat necrosis with a mixed inflammatory cell infiltrate. (Right) Vasculitis is another common feature. Neutrophils and fibrinoid necrosis are present.

Lobular Panniculitis



Vasculitis





## TERMINOLOGY

### Synonyms

- Erythema induratum of Bazin
- Nodular vasculitis

### Definitions

- Granulomatous lobular panniculitis with vasculitis

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- Likely represents hypersensitivity reaction to systemic infection (*Mycobacterium* species, *Brucella* species, hepatitis C)

## CLINICAL ISSUES

### Epidemiology

- Age
  - Classically occurs in younger adults
- Sex
  - Occurs mostly in women

### Site

- Usually on calves
  - Sometimes on shins

### Presentation

- Multiple painful nodules
- Nodules may coalesce into larger plaques
- Often will resolve with scarring and recur
- Ulceration may occur

### Treatment

- Eradication of any underlying infection

## MICROSCOPIC

### Histologic Features

- Lobular or septolobular panniculitis
  - Involves multiple lobules
- Fat necrosis
  - Ghost-like adipocyte remnants
- Histiocytes, multinucleated giant cells are numerous
  - Granulomas are common
    - May be tightly or loosely formed
    - May or may not have central caseation
  - Histiocytes may be foamy secondary to phagocytosis of necrotic adipocytes
- Remainder of infiltrate may contain neutrophils, lymphocytes, and plasma cells
- Vasculitis of intralobular vessels
  - May affect vessels of any size
  - Infiltration of vessel wall by neutrophils
  - May or may not have fibrinoid necrosis of vessel wall
  - Reactive endothelial swelling
- Fibrosis of septa
  - With convalescence, fibrosis may involve lobules and lower dermis

## ANCILLARY TESTS

### Histochemistry

- Acid-fast bacilli
  - Staining pattern: Mycobacteria may be identified
- Gram
  - Staining pattern: Will identify gram(+) or gram(-) organisms

### PCR

- Can be performed to detect mycobacteria and other bacterial species

### Serologic Testing

- Antibody testing for hepatitis C virus may be useful if this is suspected

## DIFFERENTIAL DIAGNOSIS

### Histopathologic (Lobular Panniculitides With Vasculitis)

- Rheumatoid arthritis (neutrophilic lobular panniculitis)
  - Predominantly lobules (more than septa) consisting of central necrosis and predominantly neutrophilic infiltrate are seen
  - Leukocytoclastic vasculitis can also be seen
- Crohn disease
  - Lobular (or sometimes septal) panniculitis with neutrophilic infiltrate and occasional noncaseating granulomas
- Erythema nodosum leprosum
  - Can present as septal or lobular panniculitis with dense mixed polymorphous inflammatory infiltrate with epithelioid histiocytes (some with bubbly cytoplasm)
  - Accompanied by systemic symptoms
    - Fever
    - Malaise
    - Muscle pain
    - Joint pain
    - Lymphadenopathy
    - Insomnia
    - Weight loss
    - Peripheral neuritis
- Lucio phenomena
  - Epidermal necrosis is frequent with dense dermal and subcutaneous (lobular or septal) mixed inflammatory infiltrate with prominent involvement of thickened or edematous endothelial cells
  - Acid fast bacilli should be identifiable on special staining for mycobacteria

### Clinical

- Erythema nodosum
  - Occurs predominantly in young adults (F > M), usually on shins as hot, painful, and erythematous nodules or plaques.
  - Patients can often present with fever, aches, and arthralgias
  - Causes can include
    - Streptococcal infections
    - Sarcoidosis
    - Tuberculosis

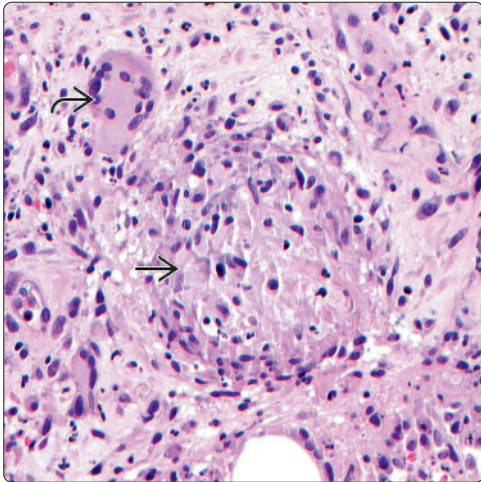
- Birth control pills
- Pregnancy
- Nonsteroidal antiinflammatory drugs
- Inflammatory bowel disease
- Subcutaneous fat necrosis of newborn
  - Occurs in neonatal period (1st few weeks after birth) as discrete hardened erythematous nodules on back, buttocks, or lower limbs
  - It is less severe than sclerema neonatorum, which can look similar
  - Treatment involves management of hypercalcemia
- $\alpha$ -1-antitrypsin deficiency
  - Very rarely presents as panniculitis
  - When present manifests as painful, indurated, erythematous nodules on trunk or extremities in 3rd or 4th decade of life
  - Mutations in *GSTP1* (PI) gene on chromosome 14q32.1 (most are of ZZ phenotype)
- Pancreatic panniculitis
  - Associated with acute pancreatitis or pancreatic carcinoma
  - May have systemic signs or symptoms (polyserositis, arthritis, eosinophilia, leukemoid reaction)
  - Tends to present on lower trunk or lower extremities as painful, indurated, erythematous nodules
- Sarcoidosis
  - Can present as erythema nodosum-like nodules on shins
  - Is referred to as Lofgren syndrome when presenting as erythema nodosum-like nodules along with bilateral hilar lymphadenopathy, polyarthralgias
- Lupus panniculitis (a.k.a. lupus profundus)
  - Can occur at any age, usually presenting on face, although it can occur at any site

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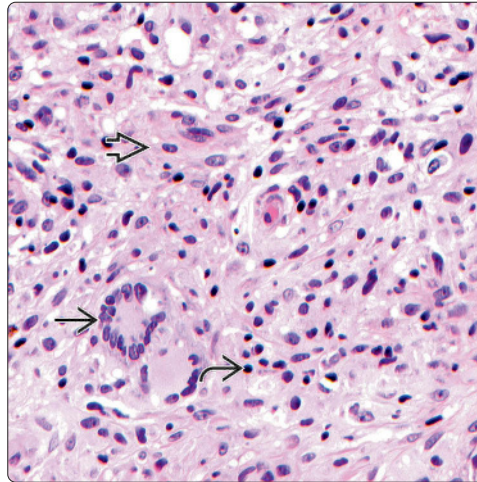
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**Granuloma**

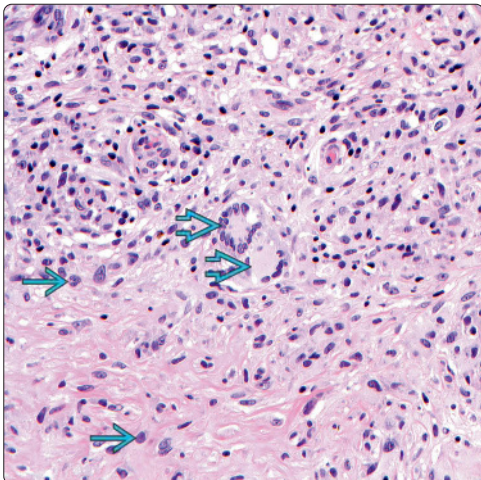


**Multinucleated Giant Cells**

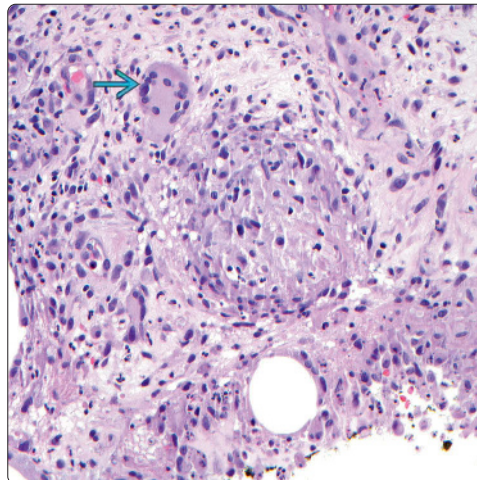


(Left) The mixed inflammatory infiltrate consists of lymphocytes, plasma cells, neutrophils, and histiocytes. Granulomas may be present with multinucleated giant cells. (Right) Usually, the mixed infiltrate is more diffuse without granuloma formation. Here, you can see multinucleated giant cells with admixed histiocytes and lymphocytes.

**Mixed Inflammatory Infiltrate**

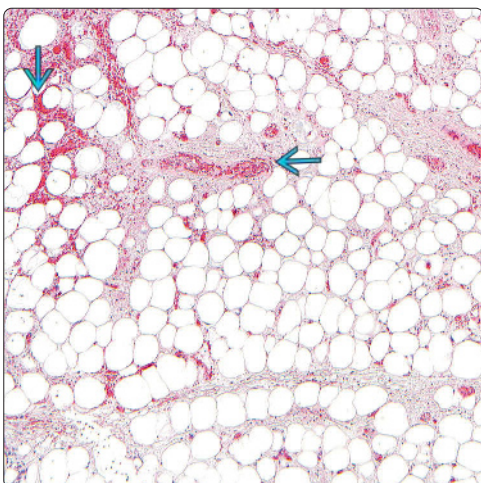


**Granulomas**

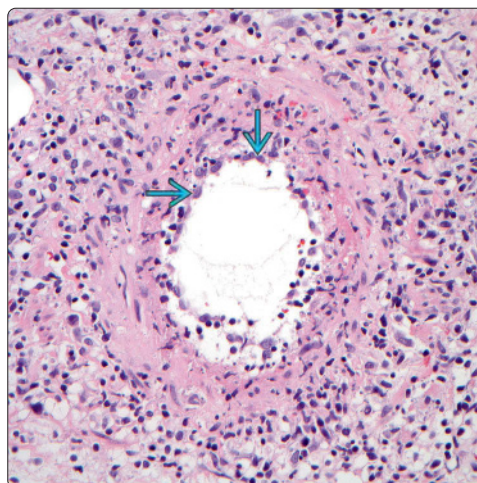


(Left) Mixed inflammatory infiltrate with predominantly mononuclear cells and multinucleated giant cells is shown. (Right) Mixed inflammatory infiltrate with prominent multinucleated giant cells and granulomas is shown.

**Red Blood Cell Extravasation**



**Vasculitis**



(Left) Lobular adipocytes with a background of sparse inflammatory infiltrate and abundant red blood cell extravasation are shown. (Right) Prominent inflammatory infiltrate involving edematous endothelial cells is shown.



# Sclerema Neonatorum

## KEY FACTS

### TERMINOLOGY

- Rare, rapid onset disease of premature neonates that is frequently fatal

### CLINICAL ISSUES

- Manifests as indurated to hardened, waxy, cool, confluent plaques of skin and subcutis bound to subjacent tissues
- Typically begins in buttock, thighs, and trunk and spreads over entire body with sparing of palms, soles, and genitalia
- Often fatal and commonly complicated by sepsis

### MICROSCOPIC

- Normal epidermis and dermis with underlying lobular panniculitis with sparse inflammation, broad septa, and fine, radially arranged needle-shaped crystal clefts within adipocytes
- No fat necrosis or calcification
- Adipocytes maintain their profile and contain radially arranged fine, needle-shaped triglyceride crystal clefts

### TOP DIFFERENTIAL DIAGNOSES

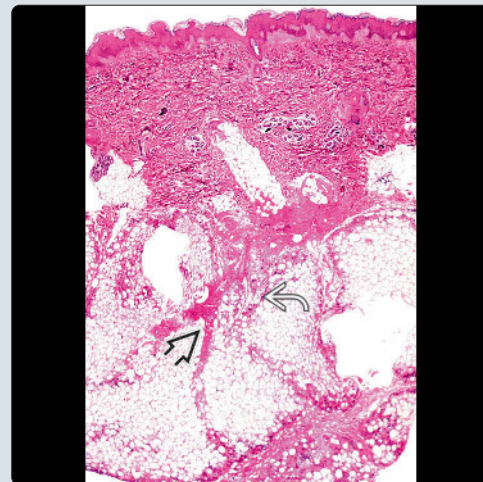
- Subcutaneous fat necrosis of newborn
  - Unlike sclerema neonatorum, there is fat necrosis, calcification, and extensive lobular lymphohistiocytic inflammation with needle-shaped crystals within both lipocytes and giant cells
- Poststeroid panniculitis
  - Occurs in young children after rapid cessation of systemic steroids resulting in extensive lobular panniculitis with needle-shaped triglyceride crystals within adipocytes and giant cells
- Cold panniculitis
  - Occurs in infants or older children after cold exposure resulting in indurated tender plaques and nodules at point of contact with cold
  - Lobular panniculitis with mixed inflammation and deep dermal perivascular lymphohistiocytic infiltrates near junction of dermis and subcutis

**Indurated, Hard, Waxy Skin**

(Left) This premature neonate with sclerema neonatorum presented within days after birth with immobile, indurated, hard, waxy skin and subcutaneous plaques with confluent zones on the posterior trunk. (Right) Sclerema neonatorum shows an unremarkable epidermis and dermis, lobular panniculitis with thickened fibrous trabeculae [A], sparse lobular inflammation [B], and no evidence of fat necrosis or calcification.

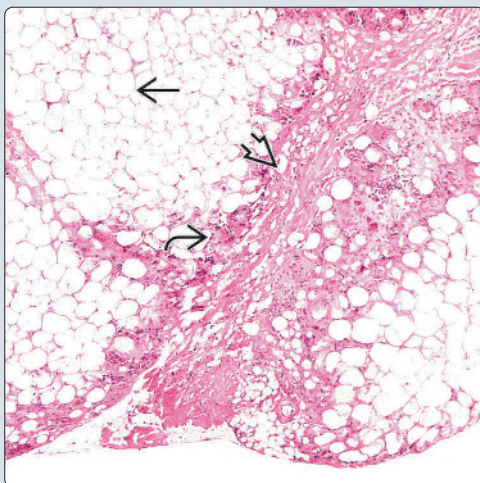


**Lobular Panniculitis on Low Power**

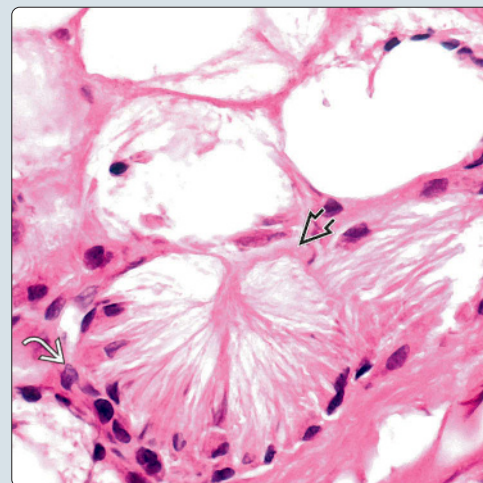


**Thick Fibrous Septa and Inflammation**

(Left) Thick fibrous septa [A], sparse lymphohistiocytic inflammation [B], and intact adipocytes [C] are seen. (Right) Adipocytes contain radial, fine, needle-like crystal clefts [D], and sparse lymphohistiocytic inflammation is present [E].



**Radial, Needle-Like Crystal Clefts**



## TERMINOLOGY

### Definitions

- Devastating rapid onset disease of premature neonates consisting of lobular panniculitis with intracellular deposition of triglyceride crystals within adipocytes
  - Thickened subcutis hinders respiration and feeding of premature neonates

## ETIOLOGY/PATHOGENESIS

### Developmental Anomaly

- 1 theory suggests thickening of subcutaneous layer due to decreased ability to mobilize fatty acids from subcutaneous adipose tissue
  - Believed to result from either defect in adipose lipolytic enzymes or one of the lipid transport mechanisms

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Very rare
- Age
  - Affects premature neonates with onset usually during 1st week of life
- Sex
  - Males and females affected equally

### Site

- Most frequently begins in buttock, thighs, and trunk but may spread to involve entire body with sparing of palms, soles, and genitalia

### Presentation

- Manifests as hardening of skin and subcutaneous adipose tissue to extent that feeding and respiration are hindered and death can occur
- Produces indurated to waxy, hard skin and subcutaneous adipose that is dry, cool, mottled, and bound to subjacent tissues
- Rapid hardening of subcutaneous fat resulting initially in plaques and later progressing to large confluent areas of involvement

### Treatment

- Supportive therapy with intensive correction of fluid and electrolyte imbalances, steroids limit spread of skin lesions, and antibiotics and exchange transfusions treat sepsis
- Warming therapy in an attempt to liquefy saturated fatty acids has not proven to be beneficial

### Prognosis

- Often fatal and commonly complicated by sepsis

## MACROSCOPIC

### General Features

- Skin and subcutis show indurated to hard, waxy plaques and larger confluent zones of involvement

## MICROSCOPIC

### Histologic Features

- Normal epidermis and dermis
- Fibrous trabeculae forming framework of subcutaneous tissue are widened and broad with diminished fat spaces
- Underlying lobular panniculitis with sparse inflammation and fine, radially arranged needle-shaped triglyceride crystal clefts within adipocytes
- Sparse inflammatory infiltrate consists of lymphocytes, histiocytes, and multinucleate giant cells and no calcification or fat necrosis
  - Minimal inflammation present attributed to poor immunological response of gravely ill neonate

### Cytologic Features

- Adipocytes maintain their profile and contain radially arranged fine, needle-shaped triglyceride crystal clefts

## DIFFERENTIAL DIAGNOSIS

### Subcutaneous Fat Necrosis of Newborn

- Self limited and occurs in healthy postterm infants within few days to few weeks after birth, affecting head and neck as well as trunk and extremities
- Circumscribed mobile plaques and nodules do not spread and disappear spontaneously or turn cystic or calcify
- Unlike sclerema neonatorum, there is fat necrosis, calcification, and extensive lobular lymphohistiocytic inflammation with needle-shaped crystals within both lipocytes and giant cells

### Poststeroid Panniculitis

- Occurs in young children after rapid cessation of systemic steroids resulting in extensive lobular panniculitis with needle-shaped triglyceride crystals within adipocytes and giant cells

### Cold Panniculitis

- Occurs in infants or older children after cold exposure resulting in indurated tender plaques and nodules at point of contact with cold
- Lobular panniculitis with mixed inflammation and deep dermal perivascular lymphohistiocytic infiltrates near junction of dermis and subcutis

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Skin biopsy of neonate showing normal epidermis and dermis with lobular panniculitis with sparse inflammation, broad septa, and fine, needle-shaped crystal clefts within adipocytes
- Fat necrosis, calcification, and prominent inflammation are absent

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2. Zeb A et al: Sclerema neonatorum: a review of nomenclature, clinical presentation, histological features, differential diagnoses and management. *J Perinatol.* 28(7):453-60, 2008



# Subcutaneous Fat Necrosis of the Newborn

## KEY FACTS

### CLINICAL ISSUES

- Present at birth or appears within 1st few days to weeks of life
- Common sites include cheeks, shoulders, buttocks, thighs, calves
- Hard, indurated nodules or plaques with overlying erythema
- May have hypercalcemia
- Self limited; generally heals without sequelae
- Morbidity can result from hypercalcemia



### MICROSCOPIC

- Lobular panniculitis
- Mostly lymphocytes, histiocytes, foreign body giant cells
- May have a few eosinophils and neutrophils
- Needle-like crystals in a radial pattern
  - Crystals represent triglycerides
- Focal fat necrosis
  - May have cyst formation

- May have calcifications

### TOP DIFFERENTIAL DIAGNOSES

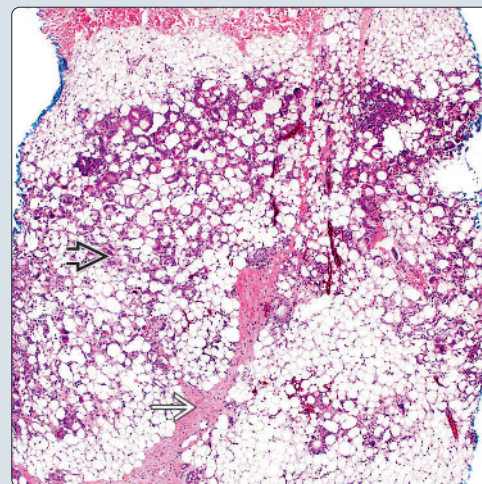
- Sclerema neonatorum
  - Clinically more diffuse with hard, wax-like skin
  - Histologically shows less inflammation and no calcification
- Cold panniculitis
  - Mixed inflammatory cell infiltrate
  - Inflammation thicker at dermosubcutaneous junction
- Lupus panniculitis
  - Rare in children
  - Often has overlying dermal and epidermal changes
  - Inflammation is predominantly lymphocytic
- Other lobular panniculitides
  - Clinical presentation helps differentiate from subcutaneous fat necrosis of newborn

(Left) Subcutaneous fat necrosis (SCFN) of the newborn is clinically characterized by firm erythematous plaques and nodules. (Courtesy E. Newman, MD.) (Right) SCFN is a lobular panniculitis as seen here. The inflammation is found within the fat lobules , sparing the septa .

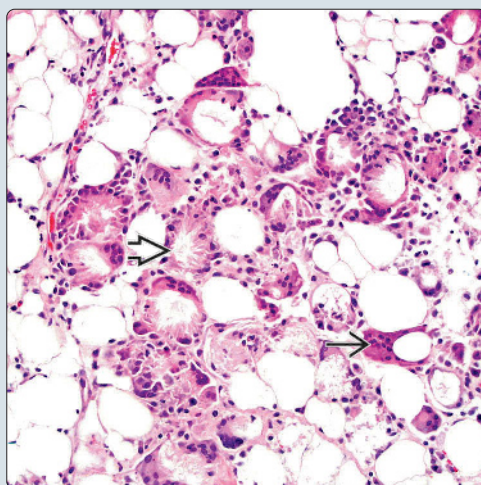
Firm Erythematous Plaques and Nodules



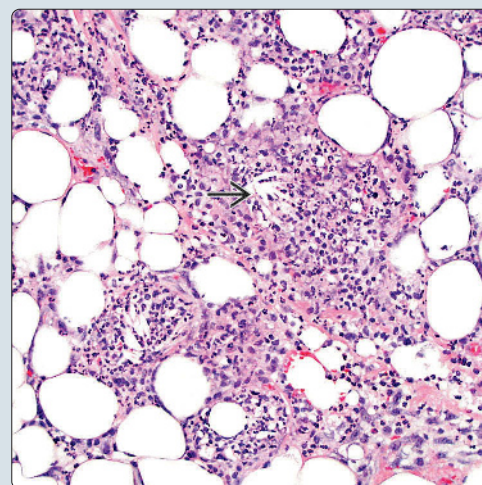
Lobular Panniculitis Sparing Septa






Chronic Inflammation With Thin Radial Lipid Crystals



Sometimes More Mixed Inflammation With Radial Crystals



(Left) The inflammation in SCFN is mostly lymphocytes, histiocytes, and foreign body type giant cells . Also seen are thin crystals arranged in a radial pattern ; these are lipid crystals. (Right) This example of SCFN has more neutrophilic inflammation than most but still has the characteristic radial crystals .



## TERMINOLOGY

### Abbreviations

- Subcutaneous fat necrosis of the newborn (SCFN)

### Definitions

- Rare lobular panniculitis seen in full-term infants

## ETIOLOGY/PATHOGENESIS

### Unknown

- Reported associations include
  - Obstetrical trauma
  - Hypothermia
  - Hypoxia
  - Anemia
  - Other causes of neonatal stress

## CLINICAL ISSUES

### Epidemiology

- Age
  - Present at birth or appears within 1st few days to weeks of life
- Sex
  - No predilection
- Ethnicity
  - No predilection

### Site

- Cheeks
- Shoulders
- Buttocks
- Thighs
- Calves

### Presentation

- Hard, indurated nodules or plaques
  - May be painful
- Overlying erythema
- Lesions can become fluctuant and spontaneously drain
- Can be solitary
- Complications include
  - Hypercalcemia
  - Hyperlipidemia
  - Thrombocytopenia

### Natural History

- Self limited
- Does not recur

### Treatment

- Medical treatment of hypercalcemia
- Occasionally cyst aspiration or incision and drainage

### Prognosis

- Generally heals without sequelae
- Healed areas may have scarring, calcification, and subcutaneous atrophy
- Morbidity or mortality can result from hypercalcemia

## IMAGING

### General Features

- Imaging generally not used unless ruling out an underlying tumor
- CT may show nonspecific thickening or nodules in subcutaneous tissue

## MICROSCOPIC

### Histologic Features

- Normal overlying epidermis
- Normal overlying dermis
- Lobular panniculitis
  - Mostly lymphocytes, histiocytes, foreign body giant cells
  - May have a few eosinophils and neutrophils
- Needle-like crystals in a radial pattern
  - Crystals represent triglycerides
- Focal fat necrosis
  - May have cyst formation
- May have calcifications

## DIFFERENTIAL DIAGNOSIS

### Sclerema Neonatorum

- Clinically more diffuse with hard, wax-like skin
- Histologically shows less inflammation and no calcification

### Cold Panniculitis

- Mixed inflammatory cell infiltrate
- Inflammation thicker at dermosubcutaneous junction

### Lupus Panniculitis

- Rare in children
- Often has overlying dermal and epidermal changes
- Inflammation is predominantly lymphocytic

### Other Lobular Panniculitides

- While many lobular panniculitides appear similar histologically, clinical presentation often assists in the proper diagnosis

### Clinical Differential Diagnosis

- **Sclerema neonatorum**
  - Rapidly progressive
  - 1/2 of patients have serious underlying illness
- **Cellulitis**
  - Patient febrile/toxic with malaise
  - Tender and warm
  - May have overlying discharge or crust

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Lobular panniculitis; needle-like crystals in a radial pattern; focal fat necrosis; may have calcifications

## SELECTED REFERENCES

1. Llamas-Velasco M et al: Panniculitis with crystals induced by etanercept subcutaneous injection. *J Cutan Pathol*. 42(6):413-5, 2015
2. Friedman SJ et al: Subcutaneous fat necrosis of the newborn: light, ultrastructural and histochemical microscopic studies. *J Cutan Pathol*. 16(2):99-105, 1989

# Post-Steroid Panniculitis

## KEY FACTS

### ETIOLOGY/PATHOGENESIS

- Occurs mostly in children
- Caused by abrupt discontinuation of high-dose systemic corticosteroids
- Original indication for corticosteroids varies

### CLINICAL ISSUES

- Indurated, erythematous or violaceous subcutaneous nodules
- Occurs mostly on cheeks
- May ulcerate

### MICROSCOPIC

- Lobular panniculitis
- Mixed inflammatory infiltrate, mostly mononuclear cells
- Foamy histiocytes
- Needle-shaped crystals radially arrayed within histiocytes and lipocytes

### TOP DIFFERENTIAL DIAGNOSES

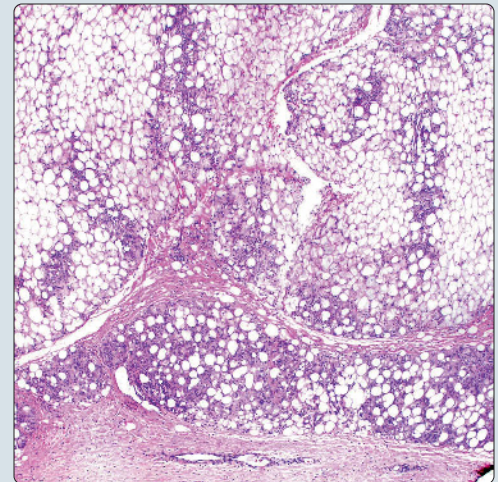
- Subcutaneous fat necrosis of newborn
  - Essentially identical histology
  - Distinguished by clinical setting of discontinuation of steroids without tapering
- Sclerema neonatorum
  - Pauciinflammatory panniculitis
  - Needle-shaped crystals radially arrayed within lipocytes
- Lupus panniculitis
  - Lobular panniculitis with lymphoplasmacytic infiltrate
  - Hyaline necrosis of fat
- Cold panniculitis
  - Lacks crystal deposition
- Gout panniculitis
  - Needles are long and slender, surrounded by granulomatous foreign body reaction
  - Needles may polarize

### Severe Atrophy of Skin, Fat, and Muscle

(Left) Steroid panniculitis shows severe atrophy of skin, fat, and muscle in a patient who received 80 mg of intramuscular triamcinolone. (Right) On scanning magnification, there is a lobular panniculitis with inflammatory infiltrates present separating individual lipocytes. The septa are not widened.

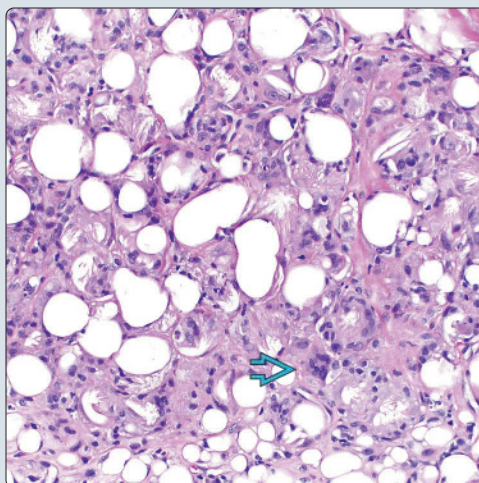


### Lobular Panniculitis

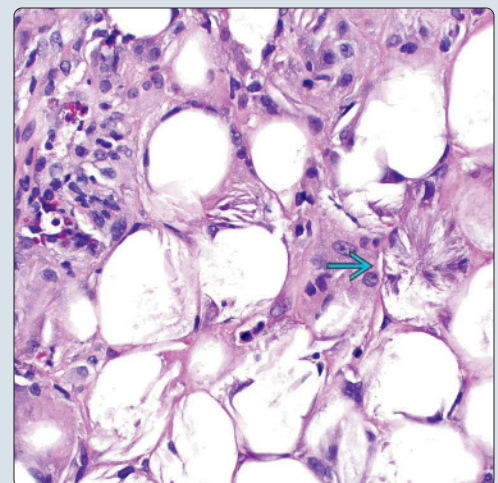


### Infiltrate Within Lobule

(Left) There is an inflammatory infiltrate consisting of lymphocytes and histiocytes within the lobule of the subcutaneous fat. Some multinucleate histiocytes are seen. (Right) Needle-shaped crystals are seen within lipocytes, in a radial array. There is background inflammation mostly by mononuclear cells. The presence of inflammatory infiltrates distinguishes this diagnosis from sclerema neonatorum.



### Crystal Deposition



## TERMINOLOGY

### Definitions

- Lobular panniculitis caused by abrupt discontinuation of steroids, typically in children

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- Caused by abrupt discontinuation of high-dose systemic steroids
  - Indications for steroids varies in literature
    - Rheumatic fever, leukemia, others

## CLINICAL ISSUES

### Epidemiology

- Overall very rare, with most reports being in children, with few cases in adults

### Presentation

- Within about 1 week of stopping high-dose steroids abruptly, patients develop erythematous indurated subcutaneous nodules
- Nodules predominate in areas of steroid-induced fat accumulation, especially cheeks

### Treatment

- Drugs
  - Resume steroids and taper slowly

### Prognosis

- Lesions tend to spontaneously regress over several weeks
- Ulceration may lead to permanent scarring

## MICROSCOPIC

### Histologic Features

- Lobular panniculitis
- Mixed inflammatory infiltrate
  - Lymphocytes, histiocytes, foam cells
- Characteristic needle-shaped crystals within cytoplasm of foamy histiocytes
- Some needle-shaped crystals may be seen within lipocytes
- Can appear identical to subcutaneous fat necrosis of newborn

## DIFFERENTIAL DIAGNOSIS

### Subcutaneous Fat Necrosis of Newborn

- Occurs in otherwise healthy newborns born at term
- May be induced by cold
- Not related to steroid discontinuation
- Histology shows identical findings
  - Lobular panniculitis with needle-shaped clefts in foamy histiocytes

### Sclerema Neonatorum

- Occurs in debilitated, preterm infants
- Widespread indurated plaques
- Not related to steroid discontinuation
- Paucinflamatory panniculitis with needle-shaped crystals in lipocytes

### Lupus Panniculitis

- Lobular panniculitis with lymphoplasmacytic infiltrate
- Hyaline necrosis of fat

### Cold Panniculitis

- Induced by cold exposure (weather, popsicles, ice)
- May occur on cheeks or on fatty areas of trunk
- Indurated erythematous plaques
- Lobular panniculitis with infiltrate of lymphocytes and histiocytes
- Lacks crystal deposition
- May also have dermal edema

### Gout Panniculitis

- Occurs more often in adults
- Needle-shaped crystals may be deposited in fat
  - Needles are long and slender, surrounded by granulomatous foreign body reaction
  - Needles may polarize

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Inflammatory infiltrates in subcutis lead to poorly demarcated erythematous indurated plaques
- Occurs in fatty areas, such as cheeks

### Pathologic Interpretation Pearls

- Needle-shaped crystals within histiocytes

## SELECTED REFERENCES

1. Llamas-Velasco M et al: Panniculitis with crystals induced by etanercept subcutaneous injection. *J Cutan Pathol*. 42(6):413-5, 2015
2. Sacchidanand SA et al: Post-steroid panniculitis: a rare case report. *Indian Dermatol Online J*. 4(4):318-20, 2013
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## KEY FACTS

**TERMINOLOGY**

- Cold panniculitis (CP)
- Synonyms include popsicle panniculitis and equestrian pernio or chilblain

**ETIOLOGY/PATHOGENESIS**

- In adults, impaired circulation and heat transfer
- In children, higher ratio of saturated fat

**CLINICAL ISSUES**

- Painful plaques or nodules on cheeks of young children or outer thighs of adult women
- Symptoms include pain, pruritus, and burning sensation

**MICROSCOPIC**

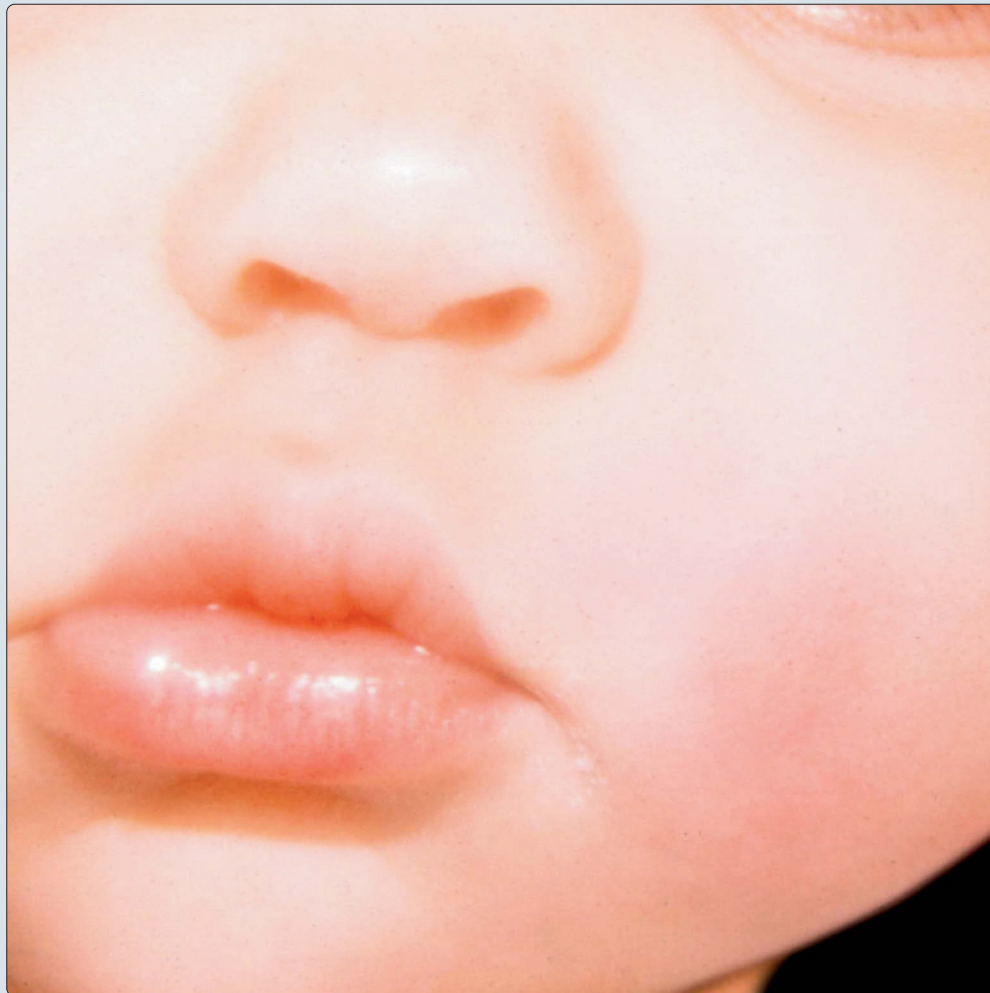
- Lymphocytic infiltrate with extension into subcutaneous fat and sometimes fat necrosis with mixed inflammation

**ANCILLARY TESTS**

- Immunohistochemistry and special stains are not helpful in distinguishing this process from pernio or cutaneous lupus erythematosus

**TOP DIFFERENTIAL DIAGNOSES**

- Cellulitis
  - Histology of early lesions demonstrates prominent edema with interstitial neutrophils while necrosis, pustules, and vasculitis may be present in late lesions
- Pernio
  - Lymphocytic infiltrate in CP prominently involves fat, while that of acral chilblain (acral pernio) does not
- Polymorphous light eruption
  - Lymphocytic infiltrate is common to both, but papillary dermal edema is uncommon in CP
- Cutaneous lupus erythematosus
  - Lupus panniculitis demonstrates more diffuse panniculitis with hyaline necrosis

**Erythematous and Indurated Plaque on Cheek of Infant**

*Cold panniculitis ("popsicle panniculitis") on the left lower cheek of a child presents as an erythematous and indurated plaque. With an appropriate history and clinical presentation, a biopsy may be unnecessary.*

**TERMINOLOGY****Abbreviations**

- Cold panniculitis (CP)

**Synonyms**

- Popsicle panniculitis, equestrian perniosis/panniculitis, equestrian chilblain, ice-pack dermatosis

**Definitions**

- Self-limiting painful erythematous plaques or nodules due to cold injury with variable histologic and clinical findings

**ETIOLOGY/PATHOGENESIS****Cold Sensitivity**

- Higher ratio of saturated to unsaturated fats in infants may result in higher freezing point of fat, potentially predisposing young children to greater cold sensitivity
- Impaired circulation and difficulty of heat transfer from warm core to outer subcutaneous fat may contribute to this process in adults

**CLINICAL ISSUES****Epidemiology**

- Sex
  - Women make up large majority of reported cases
  - Men may also rarely present with CP

**Presentation**

- CP in neonates and infants is often referred to as “popsicle panniculitis” and presents with painful, edematous erythematous plaques or nodules most often on cheeks, 48 hours following exposure to cold or ice
- In “equestrian perniosis” or “equestrian panniculitis,” adults present with erythematous or purpuric indurated plaques ± ulceration or erosion and crusting on upper lateral thighs, classically following horseback riding in winter or early spring
  - Flanks, buttocks, and lower back may also be involved
- Symptoms include pain, pruritus, and burning sensation
- Application of ice packs for chronic pain, long-distance bicycle riding, and occupational exposure to cold weather may also be causative

**Treatment**

- Options, risks, complications
  - No treatment is necessary, as CP is benign and self-limited condition

**Prognosis**

- CP is self-limited with full recovery within 2 weeks of cold exposure

**MICROSCOPIC****Histologic Features**

- Initial reports of CP described lobular panniculitis with mixed infiltrate, most prominent at junction of dermis and subcutaneous fat
  - Fat necrosis and lipophagic granulomas were also reported

- However, histology of subsequent cases, particularly those categorized as “equestrian CP” or “equestrian perniosis” demonstrate
  - Superficial and deep perivascular and periadnexal (including perieccrine and perineural) lymphocytic infiltrate, with variable features such as increased dermal mucin and extension of lymphocytic infiltrate into subcutaneous fat
- In recent small series of patients presenting with “equestrian chilblain” type of CP, predominant pattern was lymphocytic infiltrate with lymphocytic venulitis without frank fibrinoid necrosis
  - Mild superficial lobular panniculitis identified only in some cases as minor feature
  - Occasional findings included epidermal change such as vacuolar interface dermatitis, necrotic keratinocytes, and spongiosis
- Umbrella term such as CP, although occasionally misnomer, seems appropriate and reasonable

**DIFFERENTIAL DIAGNOSIS****Cellulitis**

- This is only clinical consideration
- Histology of early lesions demonstrates prominent edema with interstitial neutrophils while necrosis, pustules, and vasculitis may be present in late lesions

**Pernio (Chilblain)**

- Significant histologic overlap between these 2 conditions
  - Lymphocytic infiltrate in CP prominently involves fat, while that of acral chilblain (acral pernio) does not
  - Pernio has papillary dermal edema and less mucin deposition
- Clinical sites of involvement are helpful

**Polymorphous Light Eruption**

- Lymphocytic infiltrate is common to both, but papillary dermal edema is uncommon in CP
- Clinical sites of involvement and description are distinctive

**Cutaneous Lupus Erythematosus**

- Thickening of basement membrane is often present in cutaneous lupus erythematosus but is absent in CP
- Lupus panniculitis demonstrates more diffuse panniculitis with hyaline necrosis
  - CP may demonstrate superficial lobular lymphocytic panniculitis at junction of dermal-subcutaneous junction or fat necrosis with mixed inflammation
- Clinical history and distribution may be more helpful than histopathologic findings in providing distinction, particular in tumid lupus

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1. Ferrara G et al: Cold-associated perniosis of the thighs (“equestrian-type” chilblain): a reappraisal based on a clinicopathologic and immunohistochemical study of 6 cases. *Am J Dermatopathol*. ePub, 2016
2. Stewart CL et al: Equestrian perniosis: a report of 2 cases and a review of the literature. *Am J Dermatopathol*. 35(2):237-40, 2013
3. West SE et al: Ice-pack dermatosis: a cold-induced dermatitis with similarities to cold panniculitis and perniosis that histopathologically resembles lupus. *JAMA Dermatol*. 149(11):1314-8, 2013
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## KEY FACTS

### TERMINOLOGY

- Lobular panniculitis associated with acute or chronic pancreatitis, pancreatic pseudocysts, &/or pancreatic carcinoma

### ETIOLOGY/PATHOGENESIS

- Presumably from release and hematogeneous dissemination of trypsin, lipase, phospholipase, and amylase, leading to subsequent fat necrosis

### CLINICAL ISSUES

- Multiple tender, red to purple nodules most commonly affecting trunk, buttock, and lower extremities
- Arthralgias are commonly present (54-88%)
- Peripheral blood eosinophilia
- Primary goal is to treat underlying pancreatic condition or disease

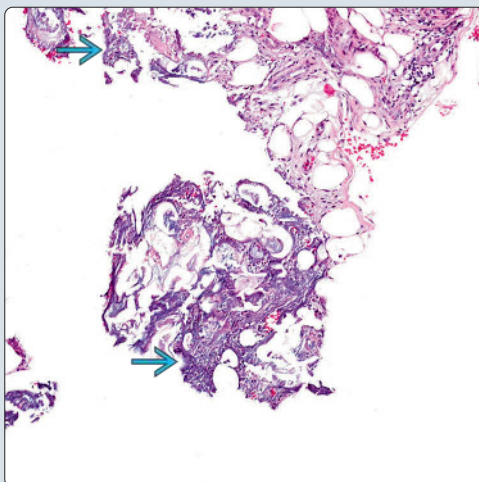
- Pancreatic disease: Acute and chronic pancreatitis, pancreatic pseudocysts, pancreatic divisum, pancreatic neoplasia [acinar cell carcinoma (most common)], pancreatic ductal carcinoma, neuroendocrine carcinoma, and intraductal papillary mucinous neoplasm

### MICROSCOPIC

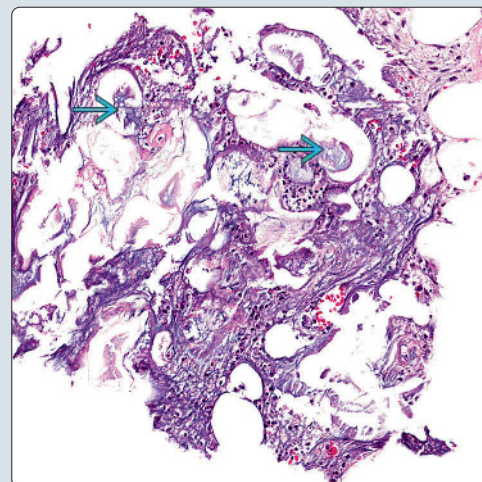
- Lobular fat necrosis with characteristic saponification (blue calcification) and "ghost" cells, which are remnants of adipocytes
- Inflammatory infiltrate consists of numerous neutrophils
- Basophilia from calcification is commonly seen
- Uninvolved fat also infiltrated by acute and chronic inflammatory infiltrate with lipid-laden macrophages

Mixed Inflammatory Infiltrate

(Left) Low-power H&E shows lobular infiltration by the mixed, predominantly neutrophilic inflammatory infiltrate. (Right) Remnants of adipocytes, a.k.a. "ghost" cells, are present as amorphic basophilic debris.

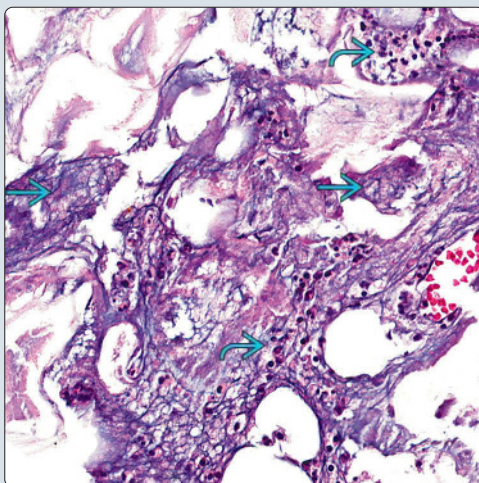


"Ghost" Cells

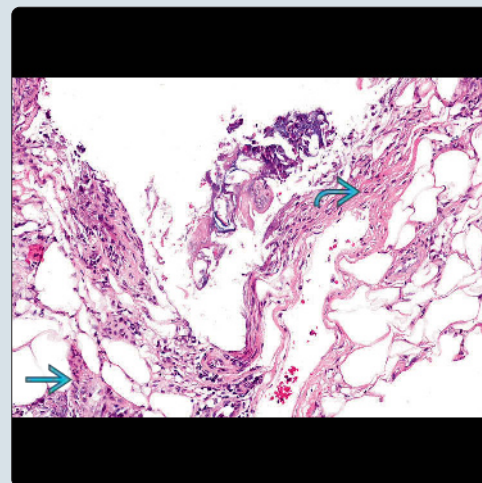


"Ghost" Cells and Neutrophils

(Left) Higher power H&E shows "ghost" cells and neutrophils. (Right) Advanced disease can show both lobular and septal inflammation.



Lobular and Septal Inflammation





## TERMINOLOGY

### Synonyms

- Subcutaneous fat necrosis

### Definitions

- Lobular panniculitis associated with acute or chronic pancreatitis, pancreatic pseudocysts, &/or pancreatic carcinoma
- Association of subcutaneous fat necrosis ("metastatic fat necrosis") with, often silent, pancreatic disease

## ETIOLOGY/PATHOGENESIS

### Etiology

- Presumably from liberation and hematogeneous dissemination of trypsin, lipase, phospholipase, and amylase, leading to subsequent fat necrosis
- Association of panniculitic skin lesion with pancreatitis was first described by Chiari in 1883

### Associations

- Underlying pancreatic disease
  - Acute and chronic pancreatitis, pancreatic pseudocysts, pancreatic divisum, pancreatic neoplasia [pancreatic acinar cell carcinoma (most common)], pancreatic ductal carcinoma, neuroendocrine carcinoma, and intraductal papillary mucinous neoplasm

## CLINICAL ISSUES

### Epidemiology

- Age
  - Middle-aged to older adults
- Sex
  - M > F

### Presentation

- Skin lesions often prevail before diagnosis of underlying pancreatic disease is determined
- Multiple tender, red to purple subcutaneous nodules or indurated plaques most commonly affecting trunk, buttock, and lower extremities
  - Rarely scalp, chest, arms are affected
  - Rarely painless
  - 10 to hundreds of lesions
  - Often involute, leaving atrophic scar
  - Can drain thick, white or brown liquid
- Arthralgias are commonly present (54-88%); can be mono-, oligo-, or polyarticular
  - Ankles most commonly affected
  - Knees, elbows, wrists, metacarpophalangeal, and metatarsophalangeal joints occasionally involved
  - Examination of joint fluid reveals presence of free fatty acids
- Pleural (25%), ascites (30%), and pericardial effusions are occasionally seen
- Medullary fat necrosis of bone can occur

### Laboratory Tests

- Peripheral blood eosinophilia (~ 60% of patients)
- Elevated serum lipase levels

### Treatment

- Primary goal is to treat underlying pancreatic condition or disease

### Prognosis

- Overall, poor prognosis with high mortality rate
  - 42% in pancreatitis associated and up to 100% in carcinoma associated
- Schmid triad: Panniculitis, arthralgias, blood eosinophilia
  - Poor prognosis

## MICROSCOPIC

### Histologic Features

- Early lesions
  - May show septal panniculitis without vasculitis or fat necrosis
- Established lesions
  - Lobular fat necrosis
  - Characteristic saponification (blue calcification) and "ghost" cells, which are remnants of adipocytes
    - "Ghost" cells: Anucleate with amorphous granular debris and may have eosinophilic border
  - Inflammatory infiltrate consists of numerous neutrophils
  - Hemorrhage common
  - Basophilia from calcification is commonly seen
  - Xanthomatous infiltrate surrounds fat necrosis
  - Uninvolved fat also infiltrated by acute and chronic inflammatory infiltrate with lipid-laden macrophages
  - Birefringent crystals have been described in mesenteric adipose tissue

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Erythema induratum
  - Has vasculitis
  - Lacks characteristic "ghost" cells and saponification of pancreatic panniculitis
- Lupus panniculitis
  - Predominantly lymphocytic infiltrate, not neutrophilic
- Behçet disease
- Infectious panniculitis
  - Acute infectious id panniculitis/panniculitic bacterid
    - From nontuberculous infectious stimuli at distant site
- Factitial panniculitis
  - From injection of foreign material
  - Often identify polarizable material in giant cells
- $\alpha$ -1-antitrypsin deficiency panniculitis
  - Genetic disorder
  - Neutrophil-rich infiltrate often extends into reticular dermis, causing "splaying" of collagen fibers

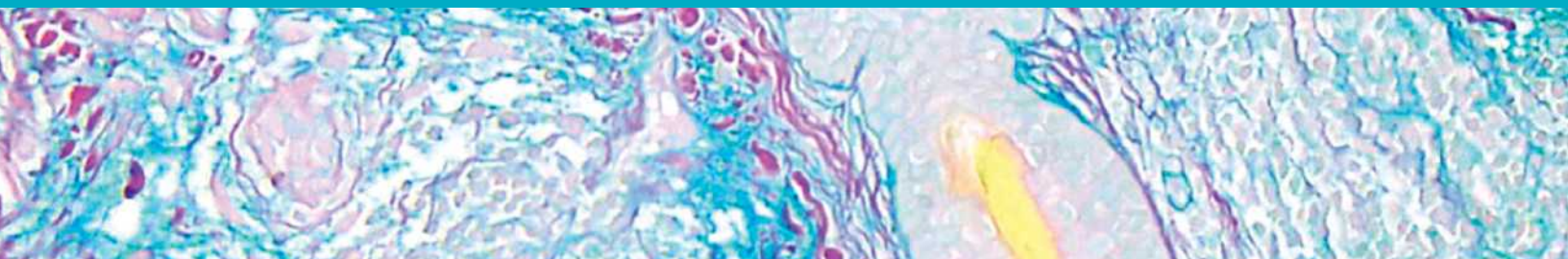
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## SECTION 6

# Connective Tissue/Soft Tissue Diseases



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## KEY FACTS

## TERMINOLOGY

- Normal scars occur immediately after injury to skin, surgical or traumatic
- Hypertrophic scars are raised but confined to boundaries of original wound
- Keloids proliferate beyond wound margin, with delayed onset

## CLINICAL ISSUES

- Hypertrophic scars and keloids both present with smooth, firm papules that may be painful or pruritic
  - Hypertrophic scars remain within wound margin; keloids do not

## MICROSCOPIC

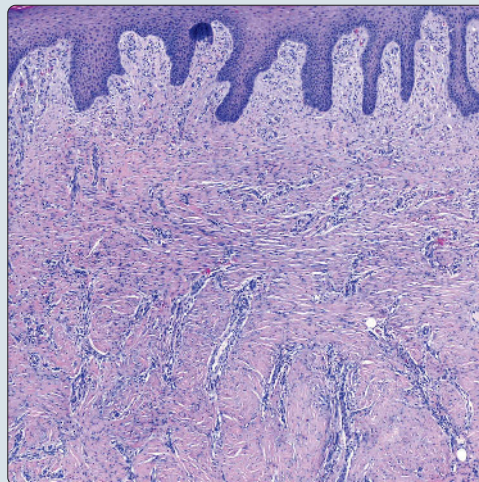
- Normal scar: Fibroblasts and collagen fibers parallel to epidermis; flattened capillary vessels perpendicular to epidermis

- Hypertrophic scar: Increased cellularity and vascularity compared to normal scar; dermal nodules with swirls of fibroblasts, blood vessels, and fine collagen fibers
- Keloid: Broad, intensely pink collagen bundles (not present in hypertrophic scars)

## TOP DIFFERENTIAL DIAGNOSES

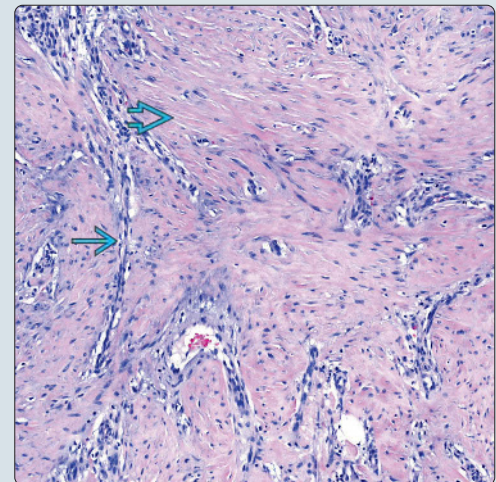
- Desmoplastic melanoma
  - Strands of spindle cells in scar-like fibrotic stroma; often lacks pigment
  - Nodular aggregates of lymphocytes are useful clue
  - Overlying or adjacent epidermis may show atypical melanocytic hyperplasia
- Dermatofibroma
  - Fibrohistiocytic cells within dermis with entrapment of collagen
  - Epidermis is often acanthotic
  - May have overlying grenz zone of sparing

Collagen Fibers and Vertically Oriented Capillaries

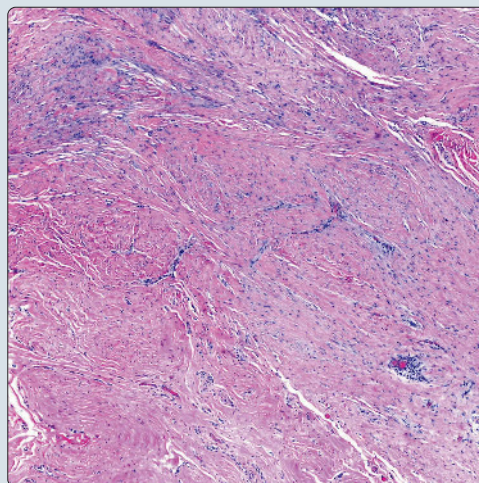


(Left) This scar demonstrates collagen fibers arranged parallel to the skin surface, collapsed capillaries oriented perpendicularly, and increased number of fibroblasts. (Right) Note the collagen fibers running parallel to skin surface [arrow] and vertically oriented blood vessels [arrow].

Collagen Fibers Running Parallel to Skin Surface

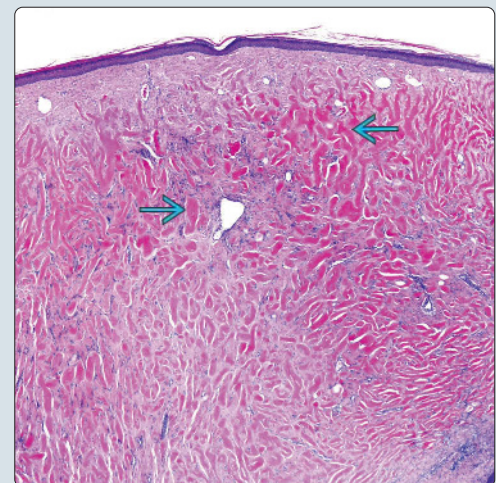


Dermal Nodule of Collagen, Myofibroblasts, and Blood Vessels



(Left) This hypertrophic scar shows a dermal nodule of fine collagen fibers, myofibroblasts, and small blood vessels. (Right) Broad bundles of intensely pink-staining, bubble gum-like collagen fill the dermis [arrow] in this biopsy of a keloid.

Broad Bundles of Pink Collagen of Keloid



## TERMINOLOGY

### Definitions

- Normal scars occur immediately after injury to skin, surgical or traumatic
- Hypertrophic scars are raised but confined to boundaries of original wound
- Keloids proliferate beyond wound margin, with delayed onset
  - Hypertrophic scars and keloids are considered to be on spectrum of aberrant wound healing

## ETIOLOGY/PATHOGENESIS

### Wound Healing

- Complex process that starts with immediate hemostasis and inflammatory phase, then remodeling; hypertrophic scars and keloids deviate from this orderly sequence for reasons that are yet known
  - Risk factors for keloid formation include infection, wound tension, foreign material, and darkly pigmented skin

## CLINICAL ISSUES

### Presentation

- Hypertrophic scars and keloids both present with smooth, firm papules that may be painful or pruritic
  - Favor earlobes, upper trunk, and shoulders
- Both occur following trauma to skin, although keloids may occur without any apparent injury to skin
- Hypertrophic scars remain within wound margin
- Keloids extend beyond borders of wound, with active pushing edges and somewhat flattened center

### Treatment

- No single effective treatment is available; options include intralesional corticosteroid injections, excision, radiation therapy, as well as various other modalities

### Prognosis

- Hypertrophic scars have tendency to regress spontaneously over many months to years
- Keloids rarely resolve spontaneously and frequently recur following treatment

## MICROSCOPIC

### Histologic Features

- Normal scar
  - Nonspecific dermal fibroblastic proliferation, associated with epidermal atrophy (or pseudoepitheliomatous hyperplasia, if recent scar)
  - Fibroblasts and collagen fibers parallel to epidermis; flattened capillary vessels perpendicular to epidermis
- Hypertrophic scar
  - Increased cellularity and vascularity compared to normal scar
  - Dermal nodules with swirls of fibroblasts, blood vessels, and fine collagen fibers
    - These nodules become thinner over time and collagen bundles gradually become parallel to epidermis, regressing to normal scar

- Keloid
  - Increased cellularity and vascularity compared to normal scar
  - Broad, intensely pink collagen bundles (not present in hypertrophic scars)
- Skin appendages absent in all types of scars

## DIFFERENTIAL DIAGNOSIS

### Desmoplastic Melanoma

- Overlying or adjacent epidermis may show atypical melanocytic hyperplasia
- Strands of spindle cells in scar-like fibrotic stroma; often lacks pigment
- Nodular aggregates of lymphocytes are useful clue
- S100(+) but often HMB-45 and Melan-A/MART-1 (-)
  - SOX10(+) stain

### Dermatofibroma

- Fibrohistiocytic cells within dermis with entrapment of collagen
- May have overlying grenz zone of sparing
- Epidermis is often acanthotic

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## Keloid

## KEY FACTS

## TERMINOLOGY

- Keloidal scar

## CLINICAL ISSUES

- Classic appearance of scar that extends, or grows beyond, wound site
- Although it can occur in any skin type, it typically presents in darker skin types (III-VI)
- Can present on trunk (preferentially sternal or presternal), extremities, neck, or earlobes, often sparing face, genitals, or acral sites
- Early lesions
  - Can be pink, smooth, tender, and rubbery
- Late lesions
  - Can be lighter, or even darker, in color and become more firm

## MICROSCOPIC

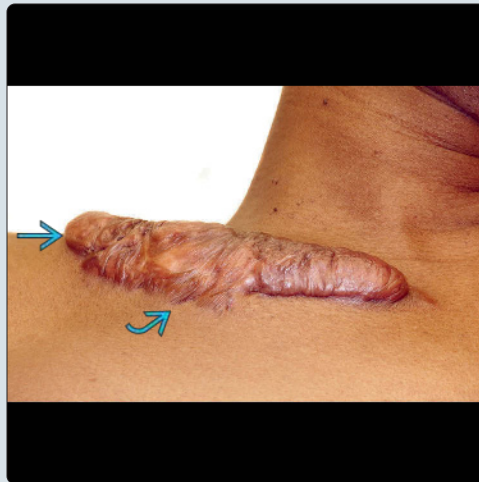
- Classically dermal fibroblasts are replaced by large bundles of "smudgy" or bubble gum-like collagen in haphazard, or random, orientation within background of hypertrophic scar
- Mast cells can be seen in the background
- Often adnexal and vascular structures are absent

## TOP DIFFERENTIAL DIAGNOSES

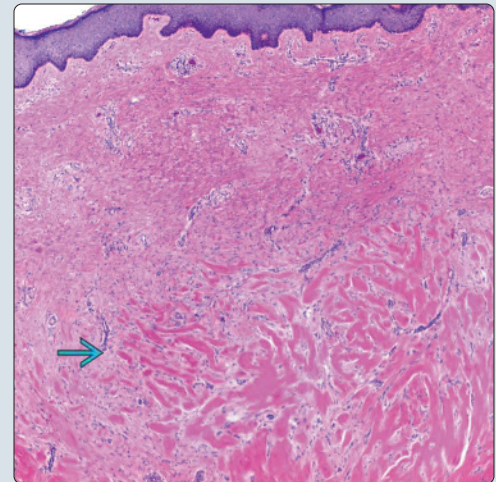
- Hypertrophic scar
  - Enlarged fibroblasts, collagen bundles in more organized pattern with associated vasculature but lacking "smudgy" or bubble gum-like collagen
- Dermatofibroma
  - Fibrous proliferation with collagen entrapment at periphery of lesion and factor XIIIa(+)
- Dermatofibrosarcoma protuberans
  - More prominent storiform pattern and CD34(+)

Pedunculated Keloid

(Left) A pedunculated, brownish-red keloid projecting above the normal skin on the upper chest of this patient is shown. Note the claw-like configurations at the periphery. (Courtesy A. Lipworth, MD.) (Right) Low-power H&E of a keloid scar consists of "smudgy" or bubble gum-like collagen bundles in the mid to deep dermis of this biopsy. (Courtesy L. Cohen, MD.)

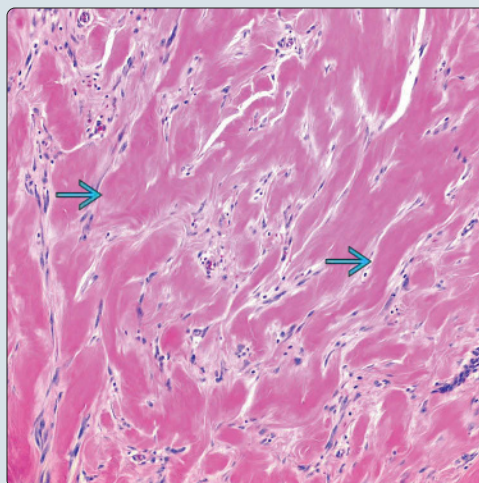


Bubble Gum-Like Collagen in Dermis

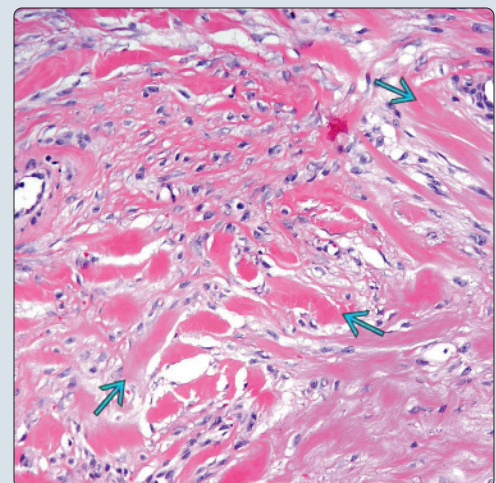


Large, Smudgy Bubble Gum-Like Collagen Bundles

(Left) High-power H&E demonstrates the "smudgy" or bubble gum-like collagen bundles. (Courtesy L. Cohen, MD.) (Right) High-power H&E demonstrates the "smudgy" or bubble gum-like collagen bundles arranged in a haphazard, or random, pattern. (Courtesy S. Wenson, MD.)



Haphazard and Random Arrangement of Thick Collagen Bundles





**TERMINOLOGY****Synonyms**

- Keloidal scar

**Definitions**

- Scar that extends, or grows beyond, wound site

**CLINICAL ISSUES****Epidemiology**

- Ethnicity
  - Although it can occur in any skin type, it typically presents in darker skin types (III-VI)

**Presentation**

- Can present on trunk (preferentially sternal or presternal), extremities, neck, or earlobes, often sparing face, genitals, or acral sites
- Can form secondary to trauma, surgery, burns, or even acne
- Tend to be delayed in onset
- Early lesions
  - Can be pink, smooth, tender, and rubbery
- Late lesions
  - Can be lighter, or even darker, in color and become more firm
- Can be itchy or painful in nature
- Rarely can become infected or develop sinus tracts or abscess

**Treatment**

- Options, risks, complications
  - Prevention of trauma in those who are predisposed is ideal
  - Treatment options vary but include
    - Intralesional Kenalog (most common)
    - Surgery (high recurrence rates)
    - Cryotherapy with probe
    - Radiation therapy
    - Laser

**Prognosis**

- Tend to persist unless treated as above

**MICROSCOPIC****Histologic Features**

- Classically dermal fibroblasts are replaced by large bundles of "smudgy" or bubble gum-like collagen in haphazard, or random, orientation within background of hypertrophic scar
- Mast cells can be seen in background
- Often adnexal and vascular structures are absent

**DIFFERENTIAL DIAGNOSIS****Histopathologic**

- Scar (classic cicatrix)
  - Fibroblasts typically oriented east to west or parallel to epidermis
- Hypertrophic scar

- Enlarged fibroblasts, collagen bundles in more organized pattern with associated vasculature but lacking "smudgy" or bubble gum-like collagen
- Dermatofibroma
  - Fibrous proliferation with collagen entrapment at periphery of lesion and factor XIIIa(+)
- Dermatofibrosarcoma protuberans
  - More prominent storiform pattern and CD34(+)

**Clinical**

- Hypertrophic scar
  - Raised scar but confined to wound margins
- Scar (classic cicatrix)
  - Flat scar also confined to wound margins
- Acne keloidalis nuchae
  - Presenting as hypertrophic scars (not keloidal) secondary to folliculitis of occipital scalp
- Dermatofibrosarcoma protuberans
  - Firm, rubbery, scar-like mass that grows slowly over several years
- Lobomycosis
  - Tends to appear as keloidal-like scars on head, neck, or extremities in endemic areas (Central and South America)

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## KEY FACTS

### TERMINOLOGY

- Multisystem autoimmune disorder with several variants affecting skin alone or skin & multiple internal organs

### CLINICAL ISSUES

- Systemic lupus erythematosus (LE): Most common systemic features are fever, weight loss, fatigue, myalgias, and lymphadenopathy
  - Organ systems affected include skin, joints, kidneys, hematologic, pulmonary, and central nervous
- Acute cutaneous LE: Cutaneous form most strongly linked with systemic disease, particularly lupus nephritis
- Subacute cutaneous LE (SCLE): Papulosquamous or annular erythematous rash predominantly in sun-exposed areas
- Chronic cutaneous LE
  - Discoid LE (DLE), hypertrophic LE, LE/lichen planus overlap, tumid LE, chilblain LE, lupus panniculitis
  - Lesions seen in chronic cutaneous forms of LE typically leave dyspigmentation or scarring

### MICROSCOPIC

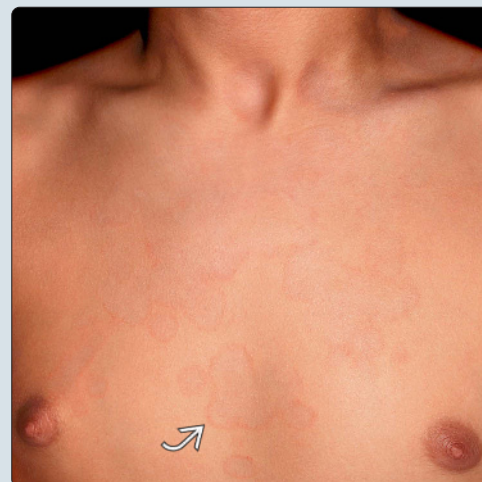
- DLE
  - Most forms of LE have histopathologic features similar to DLE, prototypic example of cutaneous LE
  - Basal layer vacuolar interface change with basement membrane thickening
  - Superficial and deep perivascular and periadnexal lymphohistiocytic infiltrate with increased dermal mucin deposition
- SCLE
  - Vacuolar interface dermatitis with dyskeratotic keratinocytes
  - Increased interstitial mucin in dermis
- Tumid LE
  - Superficial and deep, perivascular and periadnexal lymphohistiocytic infiltrate with significantly increased dermal mucin, often appreciable without special staining

### Photodistributed Erythema

(Left) Clinical photo shows acute cutaneous lupus with photodistributed erythema (as seen on the V of the chest). (Right) Subacute cutaneous lupus erythematosus (SCLE) is characterized by photodistributed annular polycyclic erythematous plaques with central clearing. This patient also had involvement on the bilateral cheeks and neck. (Courtesy K. Y. Suh, MD.)

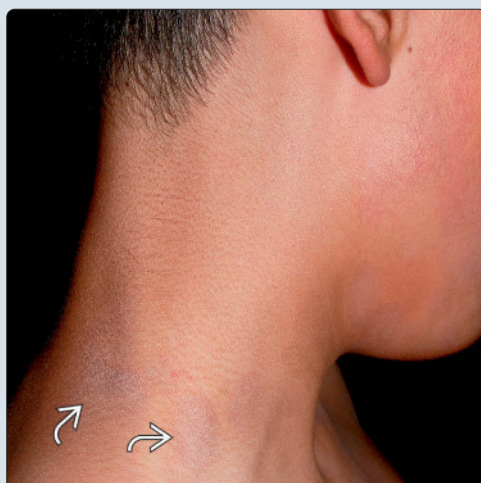


### Annular Plaques



### Photodistributed Plaques

(Left) Subacute cutaneous lupus commonly affects the sun-exposed cheeks and neck, as seen in this patient with erythematous scaly polycyclic plaques. (Courtesy K. Y. Suh, MD.) (Right) Clinical photo shows discoid LE (DLE) with typical facial erythematous dyspigmented atrophic scarred plaques on the face and involving the conchal bowl.



### Atrophic, Discoid, Scarred Plaques



## TERMINOLOGY

### Abbreviations

- Lupus erythematosus (LE)

### Definitions

- Multisystem autoimmune disorder with several variants that can affect skin alone or skin and multiple internal organs

## ETIOLOGY/PATHOGENESIS

### Autoimmunity

- Proposed complex interaction between genetically susceptible patients with environmental or infectious agent triggering or perpetuating immune response
- Numerous genes can affect overall autoimmunity; however, much focus is on genes expressing major histocompatibility complex (MHC) class II
  - MHC class II is important epitope that may recognize self-antigens that cross react with infectious agents in "molecular mimicry"
- Certain human leukocyte antigen (HLA) types tend to be more strongly associated
  - HLA-B8, HLA-DR3, HLA-DR2, HLA-A1, HLA-B15, HLA-DRw6

## CLINICAL ISSUES

### Epidemiology

- Sex
  - Predominantly affects young women (20s to 30s)
    - F:M = 6:1
    - Decreases to lower ratio in purely cutaneous forms of disease, but female predominance persists
- Ethnicity
  - Affects African American patients more often than Caucasians
    - Tends to have higher mortality and higher association with systemic symptoms in African American patients

### Presentation

- Systemic LE (SLE)
  - Most common systemic features are fever, weight loss, fatigue, myalgias, and lymphadenopathy
    - Organ systems affected include skin, joints, kidneys, hematologic, pulmonary, and central nervous, as included in criteria for classification
  - Any form of cutaneous lupus can be associated with systemic involvement
  - Nonspecific cutaneous findings include
    - Raynaud phenomenon, periungual dilated and tortuous capillary loops, livedo reticularis, urticaria, vasculitic lesions, nonscarring diffuse alopecia
- Acute cutaneous LE (ACLE)
  - Cutaneous form most strongly associated with systemic disease, particularly lupus nephritis with anti-double-stranded DNA (dsDNA) antibodies
  - Localized or generalized erythema with photosensitivity and malar rash
- Subacute cutaneous LE (SCLE)

- Psoriasiform or annular erythematous plaques predominantly in sun-exposed areas that result in dyspigmentation but not typically scarring
- Strongly associated with anti-Ro antibody
- Neonatal lupus
  - Form of SCLE in neonates born to mothers with anti-Ro antibodies, which typically presents as annular scaly plaques periorbitally and photodistributed
  - Neonates are also at risk for congenital heart block, hepatobiliary disease, and thrombocytopenia
- Chronic cutaneous LE
  - Discoid LE (DLE)
    - Indurated, atrophic, hyperpigmented plaques with follicular plugging seen typically on face, scalp, and conchal bowl
    - Heal with scarring, dyspigmentation, and alopecia if scalp involvement is present
    - 1 of most common cutaneous forms of lupus with only 5-10% of patients progressing to SLE
    - Tends to be higher risk for progression in patients with disseminated discoid lesions
  - Hypertrophic LE
    - Variant of DLE with overlying thick hyperkeratotic scaling
  - LE/lichen planus overlap
    - Syndrome with clinical and histologic features of both lichen planus and lupus erythematosus that can be difficult to distinguish from lichenoid drug eruption
    - Can occur in LE patients on antimalarials
  - Tumid LE
    - Cutaneous form of LE with low incidence of SLE occurring as edematous plaques typically on face and upper body without overlying scale or dyspigmentation
  - Chilblain LE
    - Acrally distributed dusky or purple plaques that appear or worsen in moist, cold climates
  - Lupus panniculitis and lupus profundus
    - Indurated subcutaneous plaques typically on upper extremities or upper trunk occurring from involvement of subcutis
    - If overlying lesions of DLE are present, disease is referred to as lupus profundus
- Bullous lupus
  - Bulla or vesicles appearing in patients with LE due to intense inflammation; can be seen in patients with ACLE, SCLE, or, rarely, DLE
- Rowell syndrome
  - Lesions seen in ACLE with erythema multiforme-like lesions
- Drug-induced LE
  - Rarely have skin manifestations
  - Hydralazine, procainamide, minocycline, sulfonamides, penicillin, anticonvulsants, griseofulvin (SCLE), terbinafine (SCLE), hydrochlorothiazide (SCLE), and penicillamine

### Laboratory Tests

- Serologies



# Lupus Erythematosus and Variants

- ANA (95% positive in SLE), anti-dsDNA, anti-Smith antibody (anti-Sm), antinuclear ribonucleic acid protein (rRNP), anti-La antibody
- Anti-Ro antibody (SCLE), anti-single-stranded DNA antibody, antiphospholipid antibodies (anticardiolipin antibody and lupus anticoagulant)
- Systemic involvement
  - CBC with differential to check for anemia, thrombocytopenia, leukopenia, or lymphopenia
  - Serum creatinine and urinalysis for renal involvement
- Other tests
  - Low serum complement, false-positive syphilis serologies, elevated ESR, or positive rheumatoid factor

## Prognosis

- Variable prognosis depending on type of LE and extent of systemic involvement, ranging from purely cutaneous disease to severe systemic disease with effect on overall morbidity and mortality
- Presence of multiple immunoreactants on direct immunofluorescence correlates with worse prognosis

## 1997 Update of 1982 American College of Rheumatology Revised Criteria for Classification of SLE

- For diagnosing patients in clinical studies, 4 of following 11 criteria must be met simultaneously or serially during any time period
  - Malar rash
  - Discoid rash
  - Photosensitivity
  - Oral ulcers
  - Nonerosive arthritis: Involving 2 or more peripheral joints
  - Pleuritis or pericarditis
  - Renal disorder: Proteinuria > 0.5 g/day or cellular casts
  - Neurologic disorder: Seizures or psychosis
  - Hematologic disorder: Hemolytic anemia or leukopenia or lymphocytopenia or thrombocytopenia
  - Immunologic disorder: Positive anti-DNA antibody or anti-Sm antibody or antiphospholipid antibodies (anticardiolipin antibodies), lupus anticoagulant antibodies, false-positive syphilis serologic test
  - ANA: Abnormal titer of ANA by immunofluorescence or equivalent assay at any point in absence of drugs known to induce ANAs

## MICROSCOPIC

### Histologic Features

- DLE
  - Hyperkeratosis with follicular dilation and keratin plugging often overlying thinned or atrophic epidermis with loss of rete ridge pattern
  - Basal layer vacuolar interface change over broad front with associated thickening of basement membrane that can be highlighted by PAS staining
  - Dyskeratotic keratinocytes
  - Dermal pigmentary incontinence with dermal edema and telangiectatic vessels
  - Superficial and deep perivascular and periadnexal lymphohistiocytic infiltrate
- Increased dermal mucin appreciated by increased clear spaces between dermal collagen bundles or spaces filled with amorphous blue material composed of hyaluronic acid
  - Highlighted by staining with Alcian blue or colloidal iron
- Late changes include fibrosis of dermis and loss of pilosebaceous follicular units
- Eosinophils are extremely uncommon
- ACLE
  - Early lesion of malar erythema shows basal layer vacuolar change, dermal edema, and superficial and deep lymphohistiocytic infiltrate
  - Histology can be indistinguishable from that of SCLE and commonly DLE
  - Compared with DLE, thickening of basement membrane may be less with SLE
- SCLE
  - Epidermal atrophy
  - Vacuolar interface dermatitis with dyskeratotic keratinocytes
  - Increased interstitial mucin in dermis
- Hypertrophic LE
  - Changes as seen in DLE with marked hyperkeratosis, hypergranulosis, and acanthosis
- LE/lichen planus overlap
  - Histopathologic changes of both conditions are evident on biopsy
  - Features of lichen planus include overlying compact hyperkeratosis with wedge-shaped hypergranulosis, acanthosis, and dense lichenoid lymphocytic infiltrate leading to obscuring of dermal-epidermal junction (DEJ)
    - Basal layer vacuolar change with epidermal Civatte and dermal colloid bodies are also seen
  - Features of LE include basal layer vacuolar interface change with superficial and deep perivascular and periadnexal lymphohistiocytic infiltrate with increased dermal mucin
- Tumid LE
  - Superficial and deep, perivascular and periadnexal lymphohistiocytic infiltrate with significantly increased dermal mucin, often appreciable without special staining
  - Lacks interface dermatitis typically seen in other variants of LE
  - Plasmacytoid dendritic cells in inflammatory infiltrates
- Chilblain LE
  - Epidermal changes are common, including basal layer vacuolar interface
  - Papillary dermal edema giving superficial dermis pale appearance with superficial and deep lymphocytic infiltrate
- Lupus panniculitis and lupus profundus
  - Overlying variable epidermal features, such as hyperkeratosis, basal layer vacuolar change, and epidermal atrophy or acanthosis
    - When present, lupus profundus is preferred term
  - Superficial and deep perivascular and periadnexal lymphohistiocytic infiltrate with increased dermal mucin
  - Dense lymphocytic infiltrate with occasional plasma cells in both subcutaneous fat lobules and septa with occasional follicular germinal centers

- Subcutaneous fat necrosis with characteristic hyalinization of fat lobules with occasional lipomembranous change

## ANCILLARY TESTS

### Immunofluorescence

- Lupus band test
  - Linear homogeneous band of immunoglobulins or complement deposited at DEJ with IgM being most common and IgG being most specific for LE
  - In less well-developed LE lesions, band deposition may instead be granular or reticular

## DIFFERENTIAL DIAGNOSIS

### Dermatomyositis

- Autoimmune disease with combined inflammatory disorder of muscle and cutaneous lesions classically appearing as heliotrope rash (violet periorbital discoloration)
- Symmetric erythema with poikiloderma on V of chest, Gottron sign (erythematous papules over extensor metacarpophalangeal joints), and dilated nail loop capillaries with avascular areas
- Can closely resemble SCLE, but may have increased dermal mucin compared with LE
  - Also, given that lesions clinically appear poikilodermatous, there may be mild telangiectatic vessels with pigmentary incontinence

### Lymphocytic Infiltrate of Jessner

- Multiple annular asymptomatic erythematous plaques on face, neck, and upper chest that resolve without scarring
- Epidermal changes are typically lacking
  - Dermis shows superficial and deep, tightly cuffing, perivascular lymphocyte-predominant infiltrate with scattered histiocytes and plasma cells
- Distinguished from DLE by lack of epidermal changes and lack of dermal mucin deposition

### Reticular Erythematous Mucinosi

- Rare erythematous reticular or edematous plaque-like eruption on central chest
- Typically occurs in women and without systemic involvement but possibly associated with autoimmune diseases such as diabetes mellitus, thyroid disease, and arthritis
- May represent form of tumid lupus
- Epidermis may be slightly atrophic but typically appears unremarkable
- Dermis has perivascular and periadnexal lymphocyte predominant infiltrate with abundant dermal mucin appreciated by separation between collagen bundles
- Immunofluorescence usually negative

### Lichen Planus

- Localized or generalized purple, pruritic, polygonal, papules with overlying lacy white reticulation
  - Appreciated best when lesions involve mucosal surfaces
- In developed lesions, dense lichenoid inflammation with obscuring of DEJ that becomes squamatized and develops saw tooth pattern

- Many Civatte bodies (necrotic keratinocytes) in epidermis and colloid bodies (necrotic keratinocytes) in superficial dermis
- Overlying wedge-shaped hypergranulosis and orthokeratosis
- Can be distinguished by lack of periadnexal and deep infiltrate and lack of dermal mucin

### Perniosis or Chilblains

- Painful erythematous or purplish edematous nodules present on distal extremities in patients exposed to cold, damp environments
- Patients may be at increased risk for development of LE
- Hyperkeratosis and acanthosis with prominent epidermal spongiosis overlying marked subepidermal edema with dense lymphocyte-predominant superficial and deep perivascular infiltrate
- Variable vascular fibrinoid change but lacks true vasculitis
- Chilblain LE may be favored over chilblains if positive immunofluorescence findings, interface change, or vasculitic changes

### Polymorphous Light Eruption

- Typically in young women during spring and summer months; presents as photo-induced edematous pruritic papules and plaques
  - Slightly increased risk of developing LE
- Slight patchy basal layer vacuolar interface change with epidermal spongiosis overlying exuberant subepidermal edema with possible vesiculation
- Associated superficial perivascular and periadnexal lymphocyte predominant infiltrate that can extend into deep dermis
- Lesions typically lack dermal mucin and immunofluorescence findings typical of LE

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**Lupus Panniculitis on Upper Extremity**

(Left) *Lupus panniculitis* is shown on the characteristic location of upper extremities with bound-down atrophic plaques. If overlying lesions of DLE were present, then the entity could be called *lupus profundus*. (Right) Hypertrophic DLE lesions are characterized by a dense, hyperkeratotic crust.



**Hypertrophic Discoid Lesions**

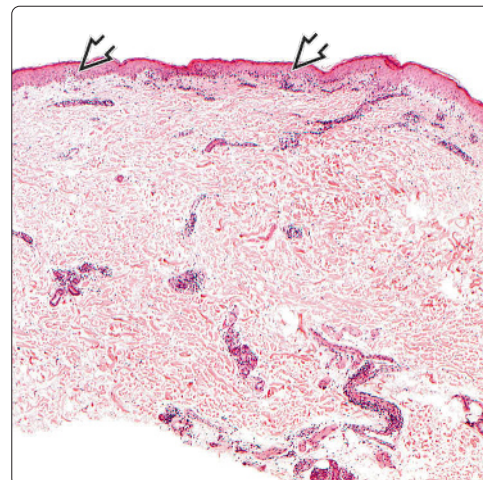


**Dyspigmentation and Scale in Discoid Lupus Erythematosus**

(Left) Facial DLE shows plaques with central atrophy and peripheral hyperpigmentation and overlying fine scale. (Right) SCLE on scanning magnification shows a lichenoid infiltrate with basal layer vacuolar changes. These changes can be appreciated at this power by obscuring of a clear dermal-epidermal junction and a superficial/deep perivascular/periadnexal infiltrate.

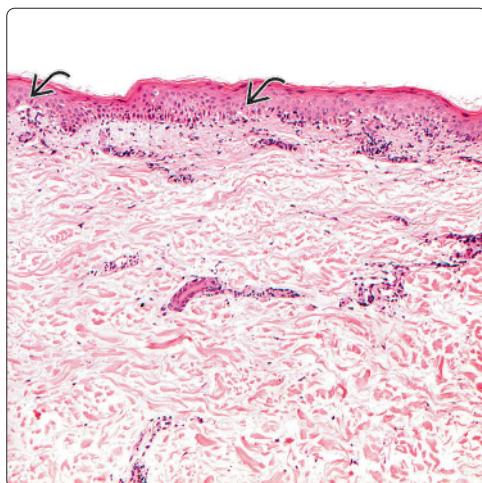


**Vacuolar Alteration in Subacute Cutaneous Lupus Erythematosus**

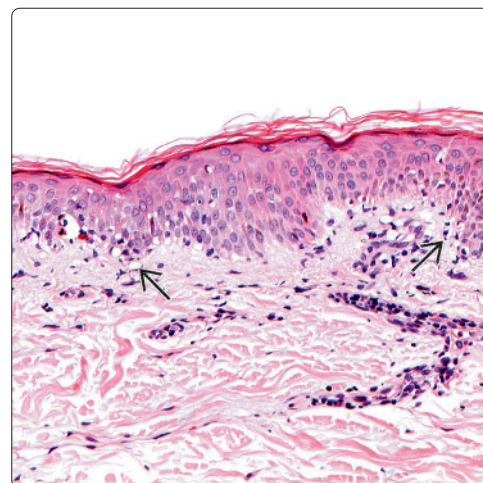


**Atrophic Epidermis in Subacute Cutaneous Lupus Erythematosus**

(Left) SCLE is distinguished from DLE by less hyperkeratosis and more marked epidermal atrophy without thickening of the basement membrane. The basal layer vacuolar change is present along with a perivascular lymphocyte-predominant infiltrate. (Right) SCLE again shows basal layer vacuolar interface change seen as clear bubbling at the dermal-epidermal junction.

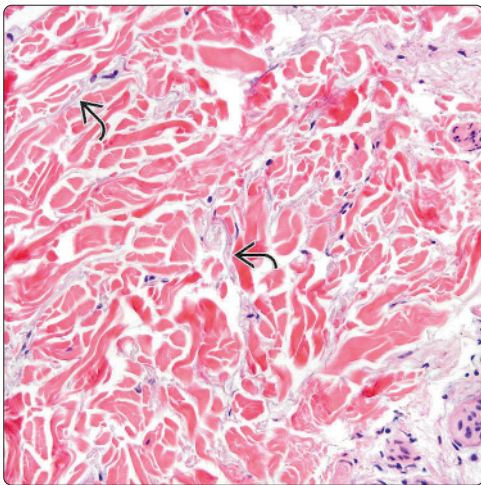


**Vacuolar Interface Change in Subacute Cutaneous Lupus Erythematosus**

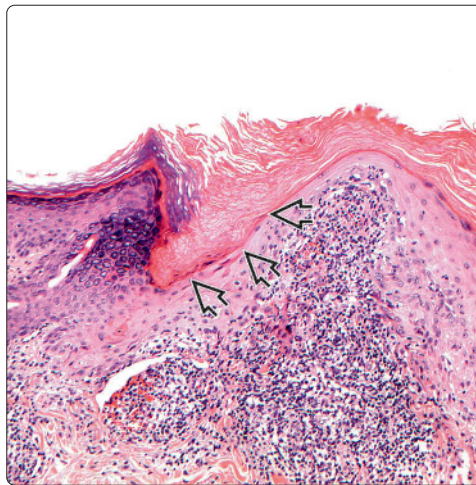




**Interstitial Mucin**

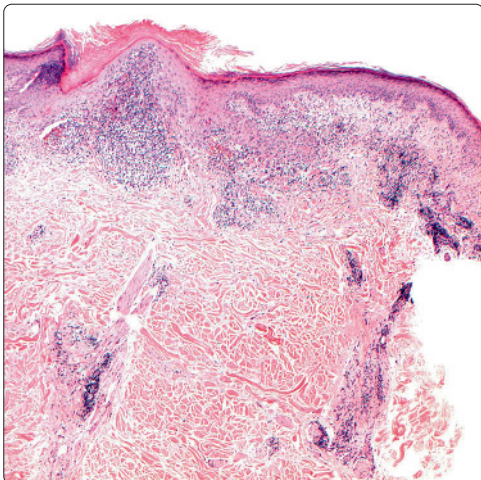


**Interface Change With Follicular Plugging**

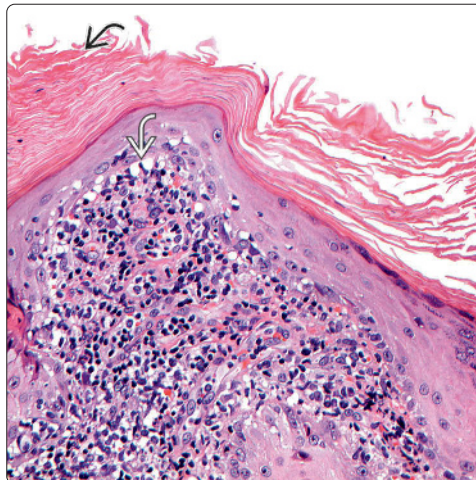


(Left) Conspicuous dermal mucin can often be seen on H&E stains alone as basophilic gray/blue strands of wispy material in between and adherent to collagen bundles [2], as in this case of SCL. Dermal mucin is a very useful feature that would favor SCL over other lichenoid dermatoses such as a lichenoid drug eruption or atrophic lichen planus. (Right) Typical features of DLE include interface change with an overlying atrophic epidermis. Note the dilated follicular orifice with prominent keratin plugging [2].

**Epidermal Atrophy, Follicular Plugging, and Interface Change**

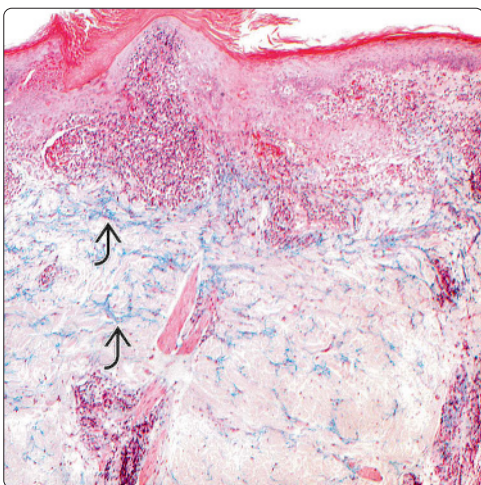


**Basal Layer Vacuolar Change**

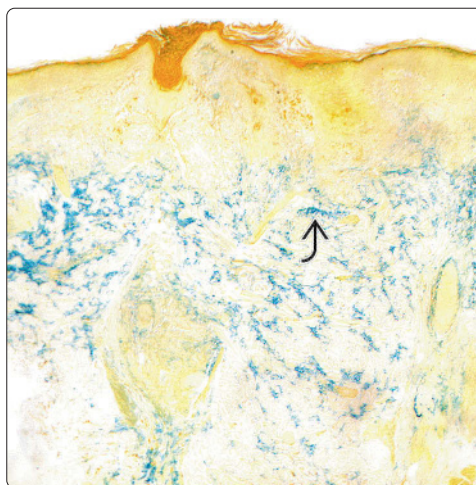


(Left) Histopathologic features of DLE include hyperkeratosis, epidermal atrophy, interface change, follicular plugging, and a superficial/deep perivascular and periadnexal lymphocytic infiltrate with increased dermal mucin. (Right) DLE shows a lichenoid lymphocytic inflammation with basal layer vacuolar interface change [2] and an overlying atrophic epidermis with hyperkeratosis [2] clinically corresponding to the scarred lesions with scale.

**Increased Dermal Mucin**



**Colloidal Iron Demonstrating Increased Mucin**

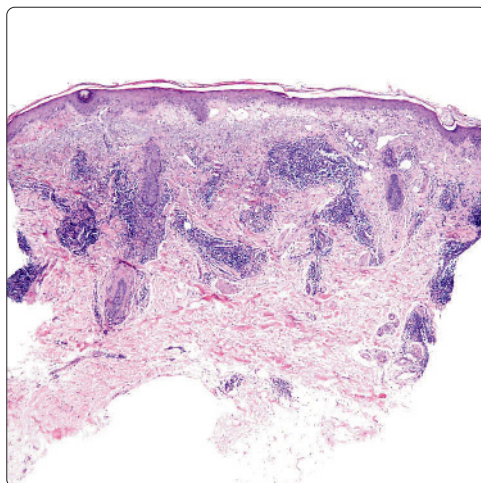


(Left) Characteristic features of DLE are noted, but the Alcian blue stain highlights the increased dermal mucin [2]. (Right) The colloidal iron stain is another method to highlight the increased dermal mucin [2] between collagen bundles. In normal skin, increased mucin is commonly seen only around adnexal structures.

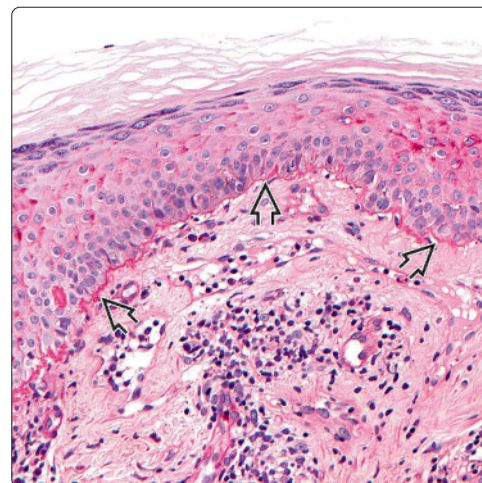


**Superficial and Deep Perivascular and Periadnexal Infiltrate**

(Left) The most notable features of DLE on low power are the superficial/deep perivascular and periadnexal infiltrate. The majority of the blue material in the superficial dermis in this biopsy was actually solar elastosis, although some mucin was appreciated on higher power. (Right) PAS stain of a DLE biopsy highlights the tortuous thickened basement membrane seen more prominently in DLE than in other forms of LE.

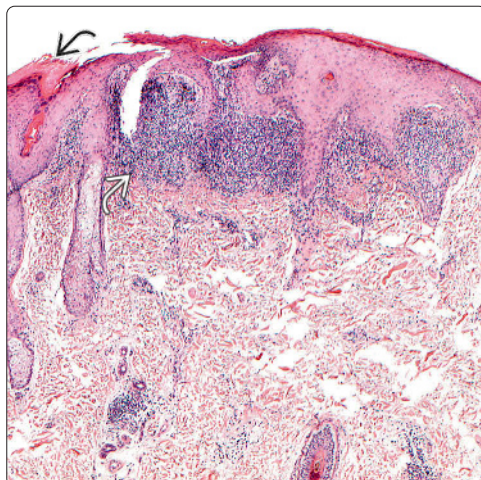


**Reduplicated Basement Membrane**

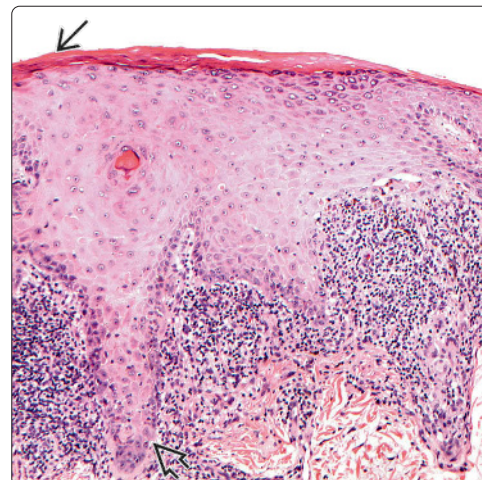


**Hypertrophic Discoid Lupus Erythematosus With Lichenoid Infiltrate and Acanthosis**

(Left) Hypertrophic DLE has the same features seen in DLE, including hyperkeratosis, follicular plugging, lichenoid infiltrate with basal layer vacuolar interface change, and superficial/deep lymphohistiocytic infiltrate with increased dermal mucin. (Right) Hypertrophic DLE is distinguished from DLE by the compact hyperkeratosis and irregular acanthosis of the epidermis.

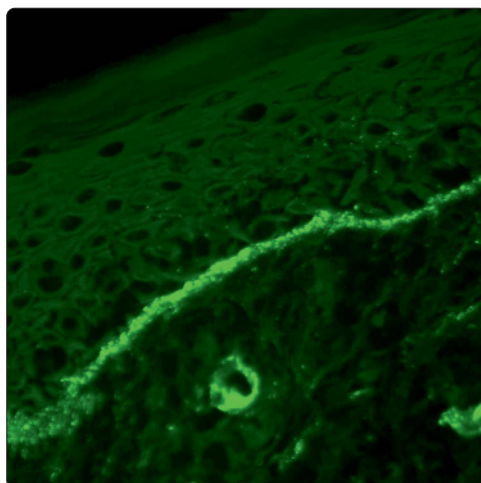


**Hyperkeratosis in Discoid Lupus Erythematosus**

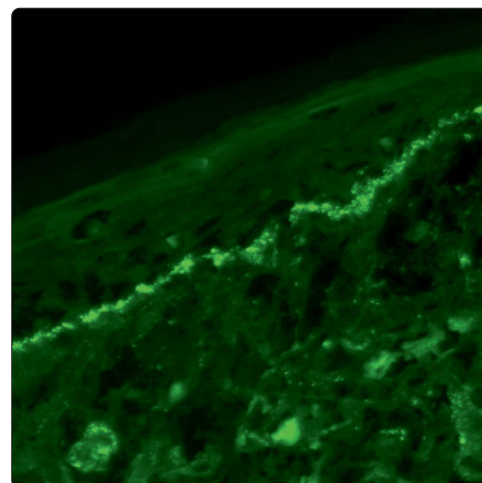


**Positive C3 at Dermal-Epidermal Junction**

(Left) Positive lupus band test shows homogeneous C3 staining at the dermal-epidermal junction. (Right) Lupus band test shows direct immunofluorescence of a skin biopsy showing a granular band of IgG at the dermal-epidermal junction.

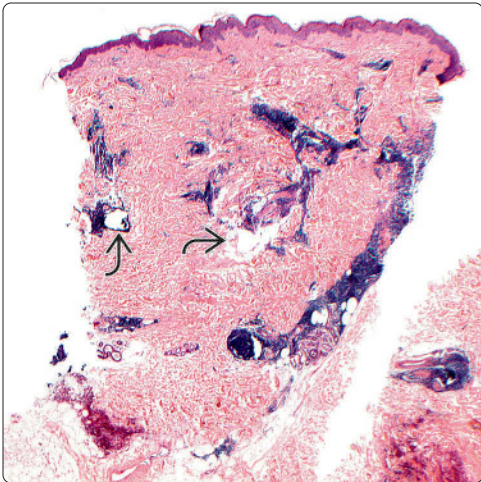


**Granular IgG at Dermal-Epidermal Junction**

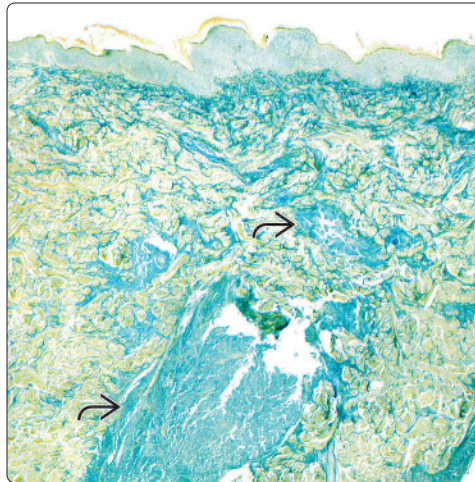




**Superficial and Deep Lymphocytic Infiltrate**

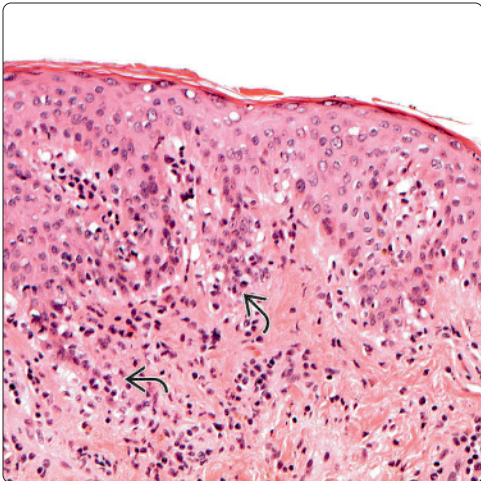


**Interstitial Mucin in Tumid Lupus Erythematosus**

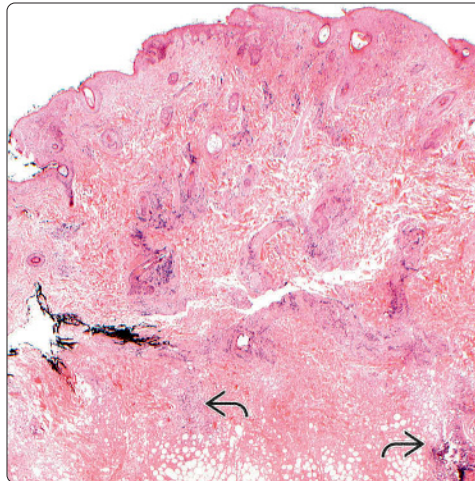


(Left) Tumid LE lacks overlying epidermal changes and shows superficial and deep perivascular and periadnexal lymphocytic infiltrates with increased dermal mucin noted on H&E by increased white spaces [2] between dermal collagen bundles. (Right) Colloidal iron staining of tumid LE highlights the abundant dermal mucin [2] dispersed diffusely between the collagen bundles in the dermis.

**Vacuolar Alteration at Junction**

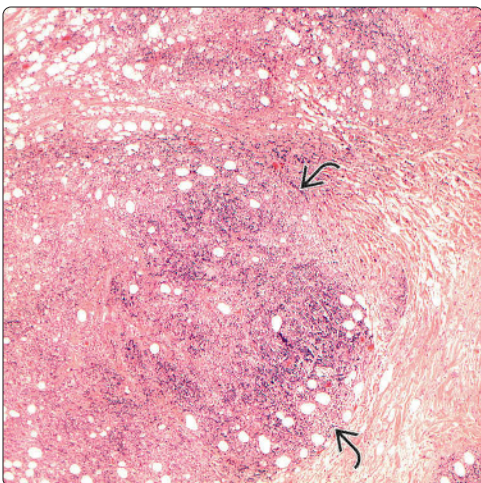


**Inflammatory Infiltrate Extending Into Panniculus**

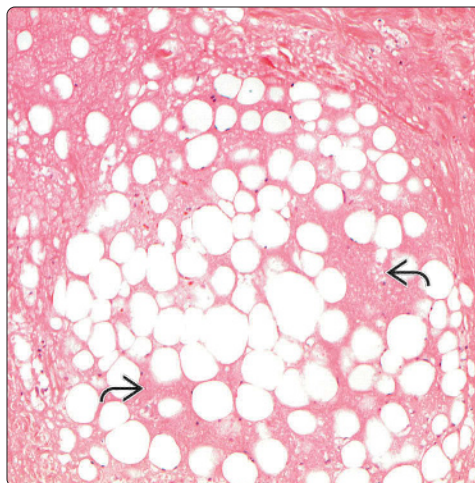


(Left) In lupus profundus, overlying epidermal changes as seen in DLE are also present. Note the interface change [2]. (Right) On scanning magnification of lupus panniculitis, note the superficial and deep periadnexal and perivascular infiltrate extending into the panniculus [2].

**Lymphoid Follicles**



**Hyaline Sclerosis**



(Left) Lupus panniculitis shows a lobular and septal panniculitis typified by dense lymphocytic infiltrates that can recapitulate lymphoid follicle formation [2]. Conversely, lupus profundus would have overlying epidermal changes of interface, atrophy, and increased dermal mucin. (Right) The feature most characteristic of lupus panniculitis is hyaline sclerosis of the fat lobules characterized by the dense eosinophilic material between adipocytes [2].



## KEY FACTS

### TERMINOLOGY

- Morphea is variant of scleroderma limited to skin, subcutaneous tissue, and underlying muscle and bone

### ETIOLOGY/PATHOGENESIS

- Environmental trigger in genetically predisposed individual leads to launch of cytokine-driven profibrotic cascade following microvascular injury

### CLINICAL ISSUES

- Classified into 5 subtypes according to varying clinical presentations
- Possibly complicated by muscular atrophy, joint contractures, and limb length discrepancies

### MACROSCOPIC

- Smooth, indurated plaques with variable postinflammatory pigmentary alteration

### MICROSCOPIC

- Early superficial and deep perivascular predominantly lymphocytic infiltrate
- Subsequent resolution of inflammation and development of obliterative sclerotic dermal collagen bundles

### TOP DIFFERENTIAL DIAGNOSES

- Systemic scleroderma
- Scleredema
- Graft-vs.-host disease, sclerodermiform chronic variant
- Scleromyxedema
- Radiation dermatitis
- Nephrogenic systemic fibrosis
- Lichen sclerosus et atrophicus

**Plaque of Morphea With Inflammatory Border**

(Left) A lesion of morphea en plaque is characteristically located on the trunk under an area of pressure (bra line). Note the violaceous peripheral rim (lilac ring) and white, sclerotic center. (Right) Pictured are lesions of generalized morphea. This patient presented with indurated plaques measuring at least 3 cm in greatest dimension over his trunk and upper and lower extremities.



**Generalized Morphea**

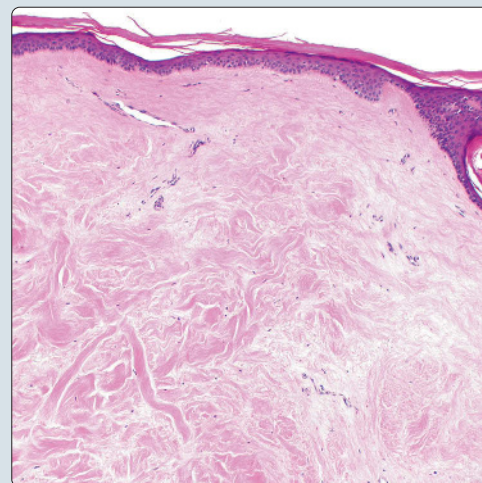


**Silhouette of Morphea**

(Left) At scanning magnification, morphea has a square or rectangular silhouette. (Right) Thick, sclerotic collagen bundles fill the papillary and reticular dermis.



**Sclerosis of Collagen**



## TERMINOLOGY

### Synonyms

- Scleroderma: Systemic sclerosis
- Morphea: Localized scleroderma

### Definitions

- Scleroderma: Diverse set of fibrosing and sclerosing disorders that result from imbalance between collagen production and destruction
- Systemic sclerosis may be diffuse or limited
  - Diffuse: Sclerosis of proximal extremities
  - Limited: Sclerosis of distal extremities
- Morphea is most common subtype of scleroderma and is clinically heterogeneous disease process localized to skin and subcutaneous tissues with possible involvement of underlying muscle and bone
  - May involve underlying central nervous system when present on face

## ETIOLOGY/PATHOGENESIS

### Multifactorial

- Precise etiology remains mystery
- Evidence suggests microvascular injury induces profibrotic cytokines following environmental insult in genetically predisposed individual
  - These cytokines lead to increased collagen production and decreased collagen destruction
- Genetic
  - Possible host factors include autoimmunity and microchimerism
  - Specific HLA class I and II alleles confer risk
- Environmental
  - Possible insults include radiation, trauma, medications, and infection (potential link to certain *Borrelia* species, particularly in Europe)

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - 0.4-2.7 per 100,000 people
- Age
  - Prevalence is equal in adults and children
    - ~ 90% of afflicted children present between 2-14 yr of age
    - Mean age of presenting adults is mid 40s
- Sex
  - About 2-4x more common in females than males
- Ethnicity
  - Affects all races, but more common in whites
    - ~ 70-80% of patients examined in ethnically heterogeneous clinical populations are white

### Presentation

- Circumscribed (morphea en plaque)
  - Most common subtype in adults
  - Patients typically present with < 3 plaques, predominantly located on trunk in areas of pressure (e.g., around waist, under bra line)
  - Lesions tend to soften over period of 3-5 yr

- Deep variant (morphea profunda): Affects dermis and subcutaneous tissue, with variable involvement of underlying fascia and muscle; overlying epidermis may not be involved
- Linear
  - Most common subtype in children
  - En coup de sabre variant: Linear induration of paramedian forehead; affects dermis with variable involvement of underlying muscle, bone, and ocular and central nervous systems
  - Parry-Romberg variant (progressive hemifacial atrophy): Patients develop atrophy of dermis, subcutaneous tissue, and underlying muscle and bone of unilateral face
  - Limb variant: Linear induration of limbs affecting dermis, subcutaneous tissue, and underlying muscle and bone causing muscle atrophy, limb length discrepancies, and joint contractures
- Generalized
  - Rare subtype that affects 7-9% of patients afflicted with morphea
  - Patients typically present with at least 4 indurated plaques measuring > 3 cm each &/or involving at least 2 of 7 anatomic sites (head/neck, extremities, anterior trunk, posterior trunk)
  - Face and hands are spared
  - Typically restricted to dermis, but can rarely involve subcutaneous tissue
  - Patients are more likely to demonstrate positive serology for autoantibodies (particularly ANA) and extracutaneous findings (e.g., arthralgias, myalgias, fatigue)
  - In contrast to those with systemic sclerosis, these patients do not suffer from Raynaud phenomenon, sclerodactyly, or nailfold capillary changes
- Pansclerotic
  - Most debilitating subtype, with significant morbidity (muscle atrophy, joint contractures, and nonhealing ulcers)
  - Patients manifest circumferential, full-thickness (skin and subcutaneous tissue, muscle, and bone) involvement of extremities
- Mixed
  - Occurs in up to 15% of morphea patients
  - Patients concomitantly express 2 or more of aforementioned subtypes
- Systemic sclerosis is clinically distinct from morphea and is subdivided on basis of extent of skin involvement
  - Limited cutaneous systemic sclerosis (insidious onset with confined involvement of skin and viscera)
    - Skin thickening distal to elbows and knees
    - Patients typically demonstrate Raynaud phenomenon for years before onset of cutaneous lesions
    - Significant late incidence of pulmonary arterial hypertension is noted
    - Includes CREST syndrome: Calcinosis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly (skin thickening distal to metacarpophalangeal joints), and telangiectasia
    - Associated with anticentromere autoantibody in ~ 70-80% of cases

# Morphea/Scleroderma

- Diffuse cutaneous systemic sclerosis (rapid disease progression with more widespread involvement of skin and viscera)
  - Skin thickening proximal to elbows or knees
  - Onset of Raynaud phenomenon within 1 yr of onset of cutaneous lesions
  - May also include features of CREST syndrome (e.g., sclerodactyly and telangiectasias)
  - Early and profound incidence of interstitial lung disease, oliguric renal failure, diffuse gastrointestinal disease, and myocardial involvement
  - Associated with antitopoisomerase 1 (a.k.a. anti-Scl-70) autoantibody in ~ 30% of cases

## Treatment

- Drugs
  - Methotrexate with systemic corticosteroids and ultraviolet A1 light phototherapy is favored for patients with extensive involvement, facial involvement, or involvement across joints
- Other therapy
  - In addition to ultraviolet A1 light, broadband ultraviolet A light, psoralen plus ultraviolet A (PUVA) light, and narrowband ultraviolet B light phototherapies have shown benefit
  - Physical therapy is recommended, particularly for patients with variants that can cause contractures (linear limb, generalized, and pansclerotic)

## Prognosis

- Patients have normal life expectancy, but may suffer significant morbidity
  - Muscle atrophy, limb length discrepancies, joint contractures, nonhealing ulcers, arthralgias, myalgias, and fatigue

## MACROSCOPIC

### General Features

- Cutaneous lesions of morphea typically present with inflammatory stage characterized by erythematous patches and plaques
- As inflammation resolves, skin lesions develop white, sclerotic center and violaceous peripheral rim (lilac ring)
- Ultimately, excess collagen deposition destroys adnexal structures and smooth, indurated plaques with variable postinflammatory hyperpigmentation result

## MICROSCOPIC

### Histologic Features

- Morphea and systemic sclerosis are clinically distinct but share identical histological features
- In early lesions
  - Superficial and deep perivascular and periadnexal predominantly lymphocytic infiltrate with rare plasma cells and eosinophils is seen in reticular dermis and at junction of dermis with subcutis
  - Endothelial cells can appear swollen
  - Collagen bundles may exhibit thickening
  - Perineural inflammation is present
- In developed lesions
  - Inflammatory infiltrate is no longer prominent

- Collagen bundles are notably eosinophilic, thickened, and crowded
  - Hypertrophic collagen bundles replace adipose tissue surrounding eccrine glands and pilosebaceous units, both of which appear entrapped and atrophic
  - Similarly, dermal blood vessels are scarce
- Collagen bundles may extend into subcutis making underlying adipose tissue appear entrapped in dermis
- Elastin fibers are retained and compressed
- Superimposed features of lichen sclerosus may be seen (homogenization of papillary dermis, hyperkeratosis)

## DIFFERENTIAL DIAGNOSIS

### Systemic Scleroderma

- Cannot be differentiated from morphea on histopathology

### Scleredema

- Hypertrophied collagen bundles are less tightly packed with intervening fenestrations containing mucin
- Prominent inflammatory infiltrate is not present at any stage of lesion

### Graft-vs.-Host Disease, Sclerodermiform Chronic Variant

- Clinical history of transplantation
- Papillary and upper reticular dermis are typically involved at earlier stage

### Scleromyxedema

- Prominent mucin deposition in upper and midreticular dermis
- Marked proliferation of irregularly arranged fibroblasts

### Radiation Dermatitis

- Clinical examination reveals presence of surface changes (xerosis, scale, hyperkeratosis, and telangiectasias) and absence of violaceous ring
- Histopathologic examination reveals atypical radiation cells, radiation-induced elastosis, and dilated superficial vessels

### Nephrogenic Systemic Fibrosis

- Clinical history of renal insufficiency and exposure to gadolinium
- Histologically similar to scleromyxedema
- May see osseous metaplasia

### Lichen Sclerosus et Atrophicus

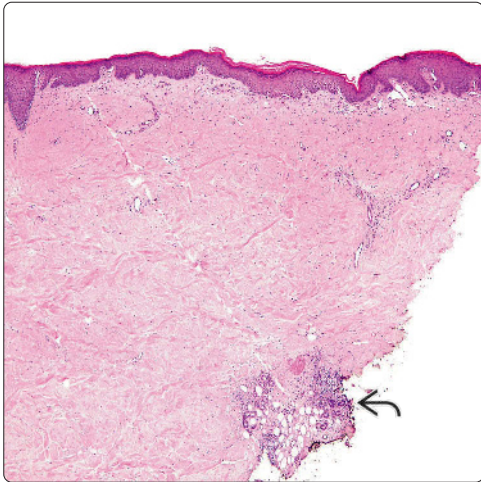
- Sclerosis is limited to papillary dermis
- Often coincides with morphea

## SELECTED REFERENCES

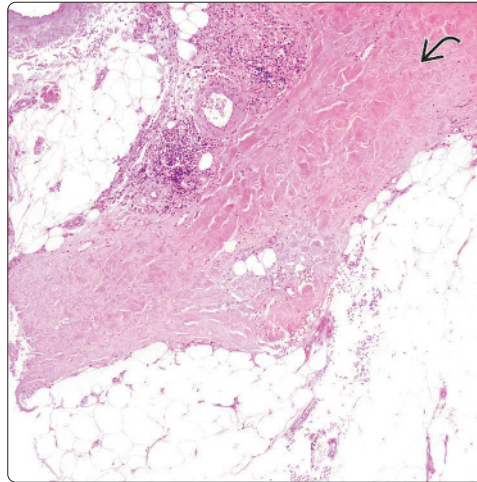
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**Superior Displacement of Adnexa**

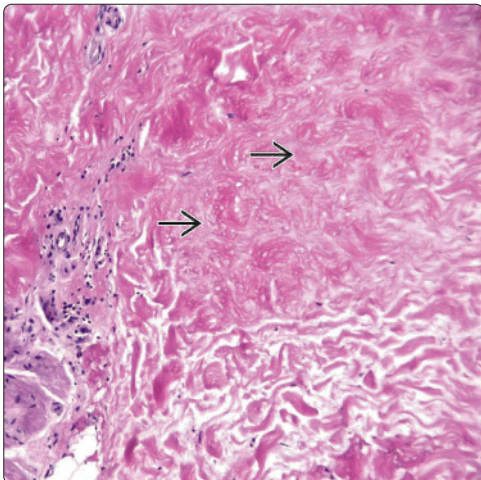


**Thick Collagen Bundles**

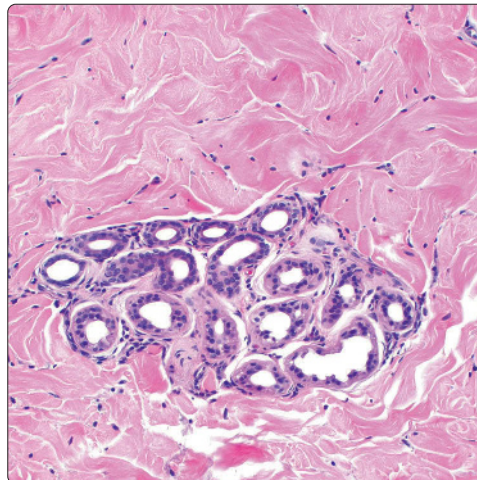


(Left) Adnexal structures [ ] can be seen at the junction between the cutis and subcutis. (Right) Collagen bundles [ ] may extend into the subcutis, making the underlying adipose tissue appear entrapped in the dermis.

**Sclerosis**

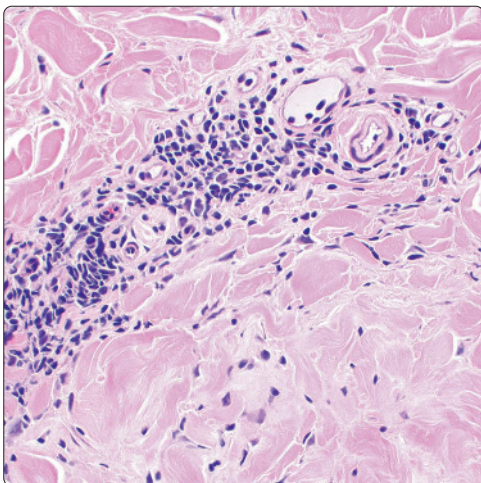


**Loss of Perieccrine Fat**

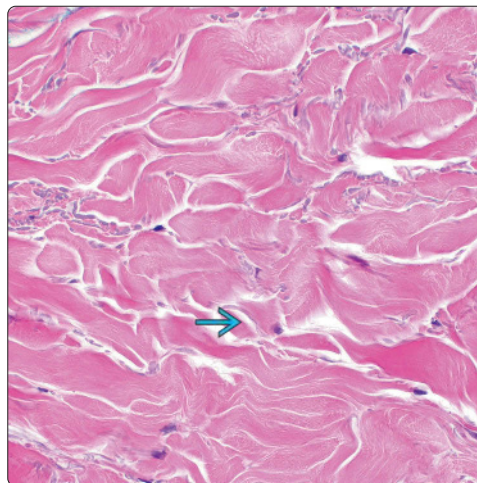


(Left) At high magnification, obliteration of the space [ ] between collagen bundles can be noted. (Right) Sclerosis replaces the fat pad normally found around eccrine sweat glands, creating the appearance of eccrine glands suspended in the mid dermis.

**Inflammatory Infiltrates in Morphea**



**Elastin Fibers**



(Left) Inflammatory lesions of morphea have lymphoplasmacytic aggregates. (Right) Elastin fibers are retained in normal numbers in morphea [ ].



## KEY FACTS

### TERMINOLOGY

- Idiopathic inflammatory myopathy (IIM) with cutaneous and systemic manifestations

### ETIOLOGY/PATHOGENESIS

- Complement-mediated microvascular injury in genetically predisposed individual following environmental insult

### CLINICAL ISSUES

- Most common IIM
- 3 types: Classical, amyopathic, and juvenile forms
- May be associated with disease in other organ systems as well as underlying malignancy
  - Cancer screening recommended

### MACROSCOPIC

- Gottron papules are pathognomonic for dermatomyositis

### MICROSCOPIC



- Most commonly demonstrates interface dermatitis with hydropic degeneration of basal layer and rare colloid bodies in papillary dermis
- Dermal mucin deposition is frequently seen as well

### ANCILLARY TESTS

- Immunohistochemistry and immunofluorescence
  - Deposition of complement C5b-9 membrane attack complex along dermal-epidermal junction and within walls of dermal blood vessels

### TOP DIFFERENTIAL DIAGNOSES

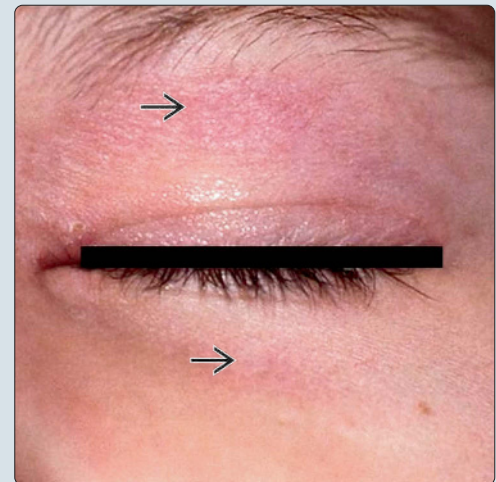
- Systemic lupus erythematosus
- Mixed connective tissue disease
- Acute and chronic graft-vs.-host disease
- Fixed drug eruption

(Left) Gottron papules  are the pathognomonic skin lesions of dermatomyositis (DM) and are characterized by violaceous, flat-topped papules and plaques on the dorsal interphalangeal and metacarpophalangeal joints. Lupus tends to skip the knuckles and affect the skin in between. (Right) Heliotrope rash  of DM is characterized by violaceous discoloration about the eyelids, particularly the upper eyelid.

Violaceous Flat-Topped Gottron Papules



Violaceous Heliotrope Rash Around Eyelids

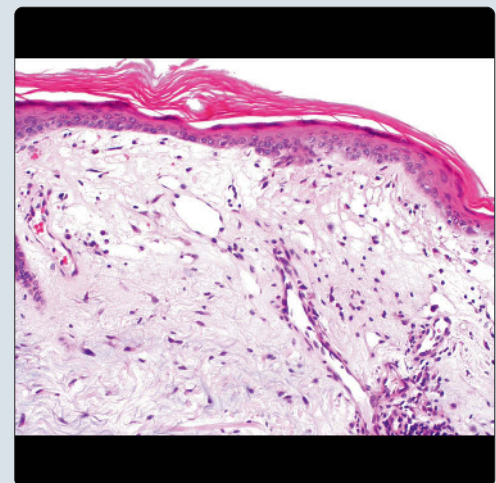


(Left) The "shawl sign" in dermatomyositis with symmetric poikilodermatous changes over the shoulders and upper outer arms. (Right) This biopsy of DM demonstrates papillary dermal edema and mucin deposition as well as a superficial perivascular lymphocytic infiltrate. There is no thickening of the basement membrane zone.

Shawl Sign



Edema and Mucin in Papillary Dermis



## TERMINOLOGY

### Abbreviations

- Dermatomyositis (DM)

### Synonyms

- Idiopathic inflammatory myopathy (IIM)

### Definitions

- IIM with cutaneous and systemic manifestations

## ETIOLOGY/PATHOGENESIS

### Multifactorial

- Microvascular injury secondary to aberrant deposition of complement C5b-9 membrane attack complex (MAC) following environmental insult in genetically predisposed individual
  - Genetic
    - Predispositions include polymorphisms of human leukocyte antigen, cytokine, and immunoglobulin genes that regulate responses to environmental agents
  - Environmental
    - Possible insults include infections, therapeutic agents, medical devices, and UV radiation
- May be paraneoplastic

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Most common among IIMs
    - ~ 8 cases per million population per year
- Age
  - Patients may present at any age; however, bimodal peaks of incidence are seen
    - Childhood (mean age: 7 years)
    - Between 45-65 years of age
- Sex
  - M:F = ~ 1:2
- Ethnicity
  - No apparent race predilection

### Presentation

- Classical DM
  - Subacute symmetric proximal muscle weakness and characteristic cutaneous lesions that may precede, overlap, or follow myopathy
- May be associated with disease in other organ systems as well
  - Joints, gastrointestinal tract, heart, lungs
  - Underlying malignancy seen in ~ 15-25% of patients
    - Most commonly adenocarcinomas of ovary, gastrointestinal tract, breast, and lung; lymphomas
    - Screening for cancer is recommended; however, there is no consensus regarding manner and frequency of screening
- Amyopathic DM (a.k.a. DM sine myositis)
  - About 10-20% of patients with DM manifest skin findings for ≥ 6 months without myopathy
- Juvenile DM

- Manifests before 18 years of age
- Similar to classical DM, except more commonly associated with calcinosis cutis, cutaneous ulcerations, and vasculopathy and less commonly with malignancy

### Treatment

- Drugs
  - Mainstay of treatment for muscle disease remains systemic corticosteroids
    - Less effective in treating cutaneous disease
  - Early initiation of oral steroid-sparing drugs is advisable and benefits skin disease
    - Methotrexate and mycophenolate mofetil are primarily used
    - Intravenous immunoglobulin, antimalarials, and various immunosuppressants have been used with varying results
  - Topical modalities may also help to lessen systemic corticosteroid doses
    - Agents include corticosteroids, antimalarials, and immunosuppressants
  - Treatment of amyopathic DM is controversial
    - Some clinicians favor conservative approach
    - Others recommend aggressive treatment with aforementioned agents in effort to thwart progression to myositis
- Other therapy
  - Lesions of DM are photosensitive
    - Daily broad-spectrum sunscreen use (with sun protective factor > 30) is advisable
  - Treatment of underlying malignancy may significantly benefit connective tissue disease

### Prognosis

- Data are limited due to relative rarity of DM
- Best in juvenile DM
- Worst in malignancy-associated DM
- Other poor prognostic signs include
  - Older age at disease onset
  - Longer duration of symptoms before making diagnosis
  - Initiating treatment after 24 months of muscle weakness
  - Progressive disease
  - Cardiac or pulmonary involvement

## MACROSCOPIC

### Gotttron Papules

- Pathognomonic for DM
- Violaceous flat-topped papules and plaques on dorsal interphalangeal and metacarpophalangeal joints
  - May develop central atrophy and telangiectasia over time

### Gotttron Sign

- Symmetric macular violaceous erythema on dorsal interphalangeal or metacarpophalangeal joints, olecranon process, patella, and medial malleoli

### Heliotrope Rash

- Violaceous discoloration around eyes (particularly upper eyelid), may have eyelid edema



## Shawl Sign

- Symmetric macular violaceous erythema involving nape of neck, shoulders, and upper back

## V Sign

- Symmetric macular violaceous erythema involving anterior neck and upper chest

## Linear Extensor Erythema

- Confluent erythematous macules on extensor surfaces of legs, thighs, arms, fingers, hands, and feet

## Mechanic Hands

- Hyperkeratosis, scaling, and horizontal fissuring of bilateral palms and fingers reminiscent of irregular, dirty-appearing lines seen in laborers

## Other

- Periungual telangiectasias
- Cuticular hypertrophy
- Poikiloderma (sign of disease chronicity)
- Nonscarring alopecia
- Erythroderma
- Vesiculobullous lesions or vasculitis
- Livedo reticularis

## MICROSCOPIC

### Histologic Features

- Often observe interface dermatitis
  - Hydropic degeneration of basal layer, with scattered colloid bodies in papillary dermis
- Minimal thickening of basement membrane and increased dermal mucin production typically seen as well
- Occasionally note mild thickening of collagen bundles (sclerodermoid change)
- At times, changes may be more subtle
  - Sparse superficial perivascular lymphocytic infiltrate
  - Edema and mucin in superficial dermis
- Biopsy of Gottron papule additionally reveals
  - Mild hyperkeratosis
  - Acanthosis
  - Papillomatosis
- In contrast, biopsy of poikilodermatous area reveals
  - Thinning of epidermis
  - Melanin incontinence
  - Dilatation of superficial vessels
- Other less commonly seen cutaneous features may be present in DM
  - Subepidermal vesiculation
  - Lobular panniculitis
  - Dystrophic calcification (more common in juvenile DM)

## ANCILLARY TESTS

### Immunohistochemistry

- Deposition of complement C5b-9 MAC along dermal-epidermal junction is indicative of DM
- Dermal vascular deposition of MAC is also seen

### Immunofluorescence

- Deposition of MAC in patterns seen with immunohistochemical stains

- Lupus band test is classically negative

## DIFFERENTIAL DIAGNOSIS

### Systemic Lupus Erythematosus

- Active (endothelial cell necrosis and intraluminal fibrin deposition) and chronic (vascular ectasia and decreased vascular density) vascular damage favor DM
  - However, DM is often histopathologically indistinguishable from systemic lupus erythematosus (SLE)
- Clinical and laboratory data are necessary to make distinction

### Mixed Connective Tissue Disease

- Sclerodermoid tissue change is fairly common in mixed connective tissue disease, but rare in DM

### Acute and Chronic Graft-vs.-Host Disease

- Distinction may be made according to clinical context
- Increased dermal mucin is not feature of acute and chronic graft-vs.-host disease

### Fixed Drug Eruption

- Increased dermal mucin is not feature of fixed drug eruption

### Drug Eruption

- Long-term hydroxyurea can simulate dermatomyositis-like skin disease

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Associated with underlying malignancy in 15-25% cases

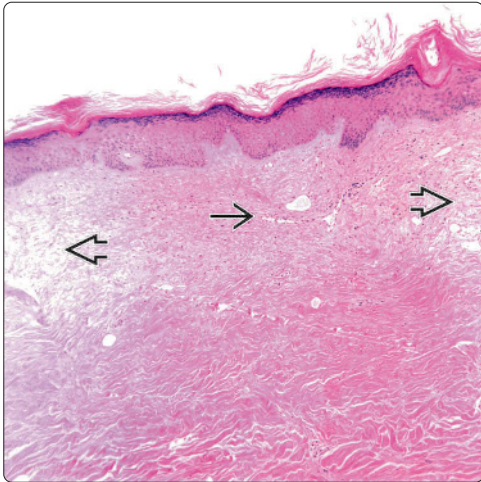
### Pathologic Interpretation Pearls

- Often histopathologically indistinguishable from SLE

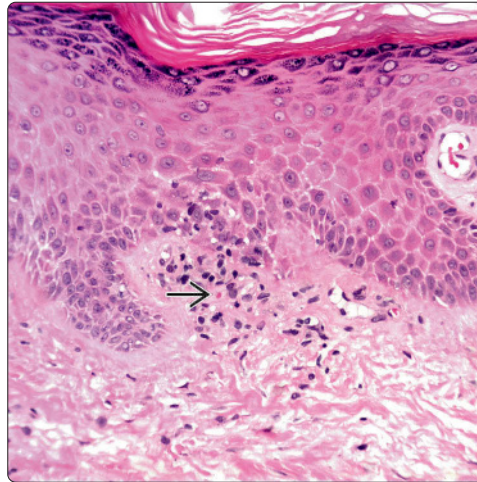
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**Superficial Dermal Edema**

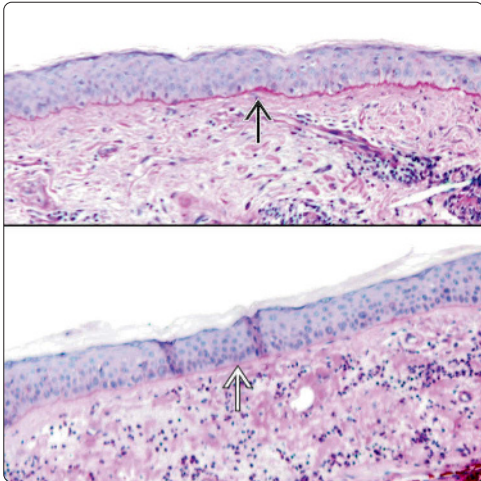


**Focal Interface Changes**

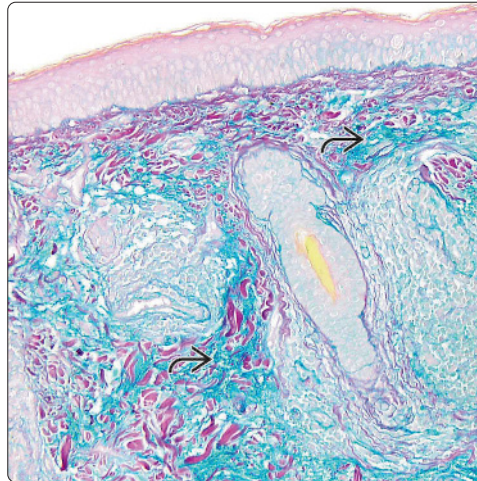


(Left) Low-power view of DM demonstrates a sparse superficial perivascular lymphocytic infiltrate and superficial dermal edema. (Right) This case of DM demonstrates focal interface dermatitis with keratinocyte death, as evidenced by a colloid body in papillary dermis.

**Thickening of Basement Membrane**

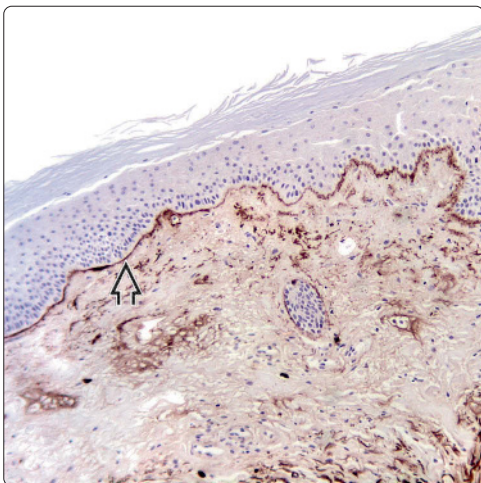


**Increased Dermal Mucin**

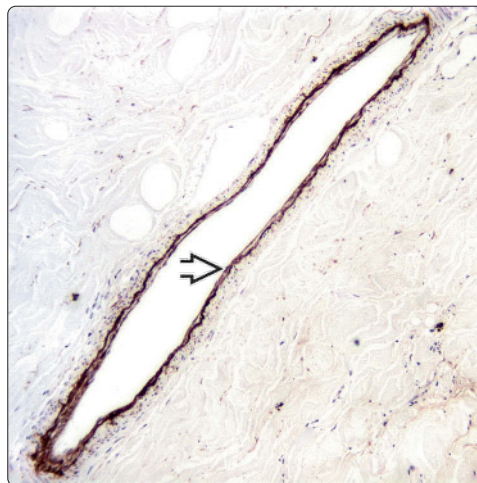


(Left) PAS stains help to contrast basement membrane of normal thickness in normal nonlesional skin versus thickened basement membrane in lesional tissue from a patient with DM. (Right) Colloidal iron stain demonstrates increased dermal mucin deposition in DM.

**Complement Deposition Along Dermal-Epidermal Junction**



**Complement Deposition Around Blood Vessels**



(Left) Membrane attack complex (MAC) immunostain highlights the deposition of complement C5b-9 MAC along the dermal-epidermal junction in cutaneous lesions of DM. (Right) MAC immunostain highlights the deposition of complement C5b-9 MAC on dermal blood vessel walls in cutaneous lesions of DM.



# Radiodermatitis

## KEY FACTS

### TERMINOLOGY

- Radiation dermatitis, radiation burn
- Side effect of tissue injury caused by irradiation of skin

### ETIOLOGY/PATHOGENESIS

- External ionizing radiation causes direct injury to epidermis and blood vessels, leading to acute and late reactions

### CLINICAL ISSUES

- Long-term surveillance is indicated for postradiation malignancies

### MICROSCOPIC

- Histologic features vary depending on stage of injury and are not pathognomonic
- Chronic
  - Hyperkeratosis, focal parakeratosis, variable epidermal atrophy or acanthosis
  - Deep and sometimes fascial fibrosis with atypical, stellate fibroblasts ("radiation fibroblasts")

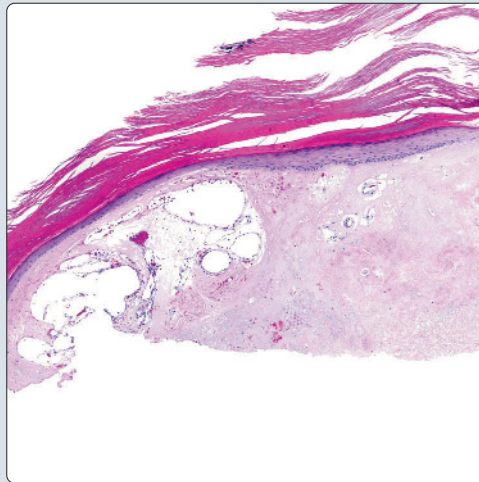
- Atypical endothelial cells with thickened blood vessel wall; telangiectasia
- Loss of appendages, especially hair follicles
- Subacute
  - Interface dermatitis with basal vacuolar changes, dyskeratotic keratinocytes, dermal melanophages, and superficial dermal perivascular lymphocytic infiltrate

### TOP DIFFERENTIAL DIAGNOSES

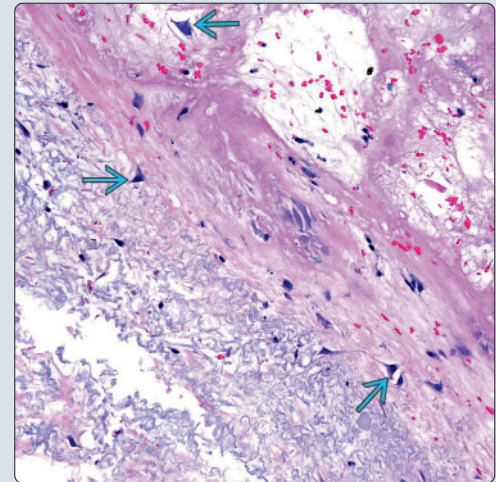
- Obtaining detailed history, including previous radiation exposure and procedures, is helpful in establishing diagnosis
- Differential of atypical fibroblasts: Lichen simplex chronicus, pressure ulcers, pleomorphic fibroma
- Differential of chronic radiodermatitis: Scleroderma, lichen sclerosis et atrophicus, infiltrating tumors
- Differential of subacute radiodermatitis: Acute graft-vs.-host disease, adverse drug eruption

**Epidermal Atrophy With Marked Hyperkeratosis**

*(Left) Marked hyperkeratosis and epidermal atrophy are noted in this low-magnification view. The dermis is sclerotic with vascular ectasia. (Right) This high-magnification view reveals dermal elastosis and sclerosis with atypical, stellate fibroblasts ("radiation fibroblasts")* [\[5\]](#)

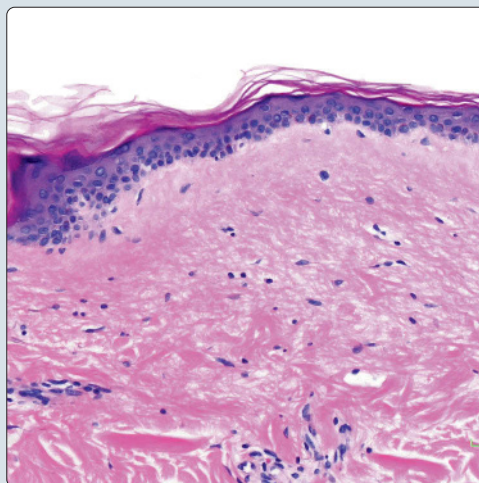


**Atypical Stellate Fibroblasts**

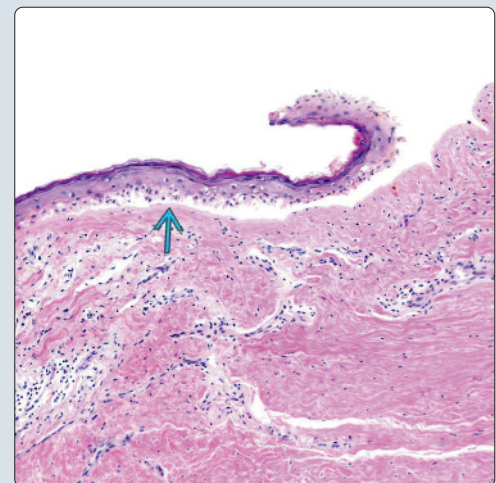


**Dermal Fibrosis of Chronic Radiation Dermatitis**

*(Left) Thickened collagen bundles are noted. Dermal fibrosis in chronic radiation dermatitis is diffuse and can be deep, even involving the fascia. (Right) Epidermis is atrophic and lifting off due to marked vacuolar change* [\[6\]](#). This is a change characteristic of subacute radiation dermatitis.



**Vacuolar Interface Dermatitis**





## TERMINOLOGY

### Synonyms

- Radiation dermatitis, radiation burn

### Definitions

- Side effect of tissue injury caused by irradiation of skin
  - Usually follows radiotherapy for underlying malignancies

## ETIOLOGY/PATHOGENESIS

### Ionizing Radiation

- External ionizing radiation causes direct injury to epidermis and blood vessels, leading to acute and late reactions
- Extent of damage is variable and depends on type of radiation, dosage, and individual factors
- May also result from prolonged exposure to fluoroscopy during procedures such as coronary angiography, embolization procedures, and catheter placements

## CLINICAL ISSUES

### Presentation

- Acute (occurring within 90 days of radiation exposure)
  - Erythema, edema, hair loss, moist desquamation, ulceration
  - Lesions are graded into 4 stages, similar to grading of burns, ranging from faint erythema and desquamation to ulceration of skin
- Chronic (occurs months to years later)
  - Poikiloderma (pigmentary changes and telangiectasia)
  - Epidermal atrophy and fragility, but skin feels indurated due to dermal fibrosis
    - Postirradiation fibrosis occurs gradually over many years; postirradiation morphea appears very similar clinically, and histopathologic exam is often necessary to distinguish between 2 entities
  - Permanent alopecia; ulceration/necrosis of soft tissue
  - Secondary skin malignancies (basal cell carcinoma, squamous cell carcinoma, atypical fibroxanthoma, and others)

### Treatment

- Acute radiation dermatitis
  - Mild cleanser, emollients, sun protection; topical steroids may help with symptoms short term
- Chronic radiation dermatitis
  - No specific, effective treatment
  - Symptomatic relief from pruritus and pain with topical corticosteroids and anesthetics/analgesics
  - Treat malignancies as appropriate

### Prognosis

- Acute reactions are usually self-limited; late changes are permanent and often slowly progressive
- Long-term surveillance is indicated for postradiation malignancies

## MICROSCOPIC

### Histologic Features

- Histologic features vary depending on stage of injury and are not pathognomonic

- Acute
  - Not biopsied routinely, as it is well recognized clinically
  - Intracellular edema and spongiosis of epidermis with necrotic keratinocytes; dermal edema, fibrin thrombi in small vessels, and hemorrhage
- Chronic
  - Hyperkeratosis, focal parakeratosis, variable epidermal atrophy, or acanthosis
  - Deep and sometimes fascial fibrosis with atypical, stellate fibroblasts ("radiation fibroblasts")
  - Atypical endothelial cells with thickened blood vessel wall; telangiectasia
  - Loss of appendages, especially hair follicles
- Subacute
  - Not well characterized clinically, but can have distinct histologic features
    - Interface dermatitis with basal vacuolar changes, dyskeratotic keratinocytes, dermal melanophages, and superficial dermal perivascular lymphocytic infiltrate

## DIFFERENTIAL DIAGNOSIS

### Acute

- Clinically, can resemble cellulitis, arthropod bite reaction, herpes zoster, fixed drug eruption, bullous disorders

### Chronic

- Differential of atypical fibroblasts
  - Lichen simplex chronicus, pressure ulcers, pleomorphic fibroma
- Scleroderma/morphea
  - Scleroderma does not typically have epidermal changes of ulceration or hyperkeratosis; also lacks atypical fibroblasts
  - May occur as complication of chronic radiation dermatitis (postirradiation morphea)
- Lichen sclerosis et atrophicus (LSA)
  - Lacks atypical fibroblasts of chronic radiodermatitis; however, be aware that LSA rarely occurs as late complication of radiation therapy within treated field
  - May resemble inflammatory breast carcinoma clinically; latter shows atypical, infiltrative tumor cells on histology
- History of radiation exposure &/or procedures is helpful in establishing diagnosis

### Subacute

- Acute graft-vs.-host disease
  - Can share features of interface dermatitis with prominent keratinocytic necrosis
- Adverse drug eruption
  - May be difficult to differentiate; clinical correlation is necessary

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## Eosinophilic Fasciitis

## KEY FACTS

## TERMINOLOGY

- Scleroderma-like disorder with symmetric thickening of fascia accompanied by mixed inflammatory infiltrate
- Induration of skin and soft tissues
- Synonyms
  - Shulman syndrome, diffuse fasciitis with eosinophilia

## CLINICAL ISSUES

- Depressed patches may exhibit groove sign
- Indentation along longitudinal aspect of superficial vein
- 30% of cases have comorbid morphea
- Patient characteristics
  - More common in women
  - Predominantly 2nd-6th decades
- May be associated with
  - Malignancy
  - *Borrelia burgdorferi*
  - Medications
  - Arthropod bites

- Vigorous exercise

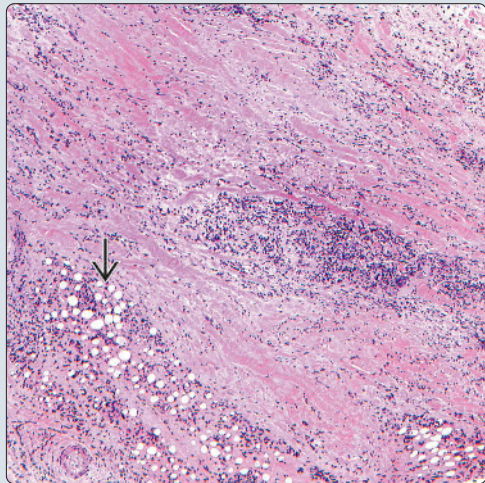
## MICROSCOPIC

- Fascial edema and thickening
- Infiltrate of eosinophils, lymphocytes, histiocytes, and plasma cells
- Eosinophils may be focal or prominent
- Thickening of adipose tissue interlobular fascia
- Sclerosis of deep dermis with atrophy of cutaneous adnexal structures
- Septal thickening may extend into skeletal muscle

## TOP DIFFERENTIAL DIAGNOSES

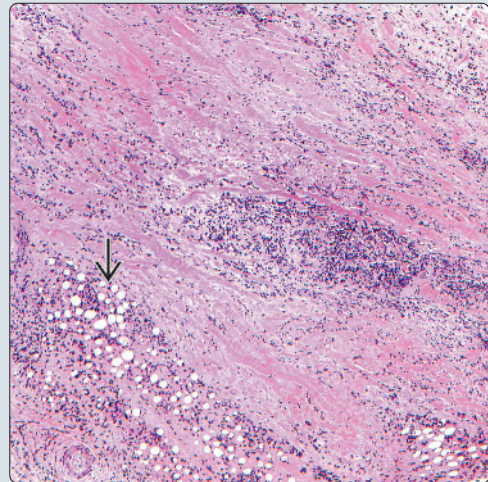
- Scleroderma
- Linear scleroderma
- Morphea profunda (subcutaneous morphea)
- Eosinophilic myositis/perimyositis
- Eosinophilia-myalgia syndrome

Skin Tightening

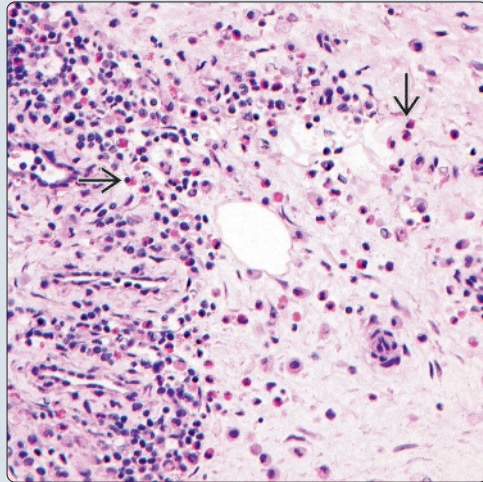
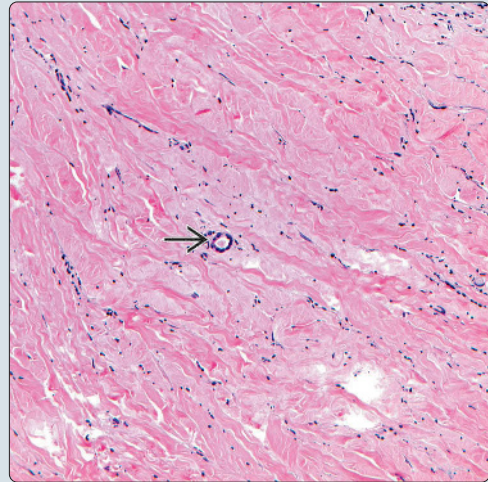
(Left) Eosinophilic fasciitis shows erythematous painful indurated skin mimicking scleroderma with inability of the patient to close his hands together. Disease was confirmed by biopsy and peripheral eosinophilia. (Right) The fascia in this case is diffusely infiltrated by chronic inflammatory cells, this time with almost no neutrophils. A small residual area of adipose tissue is present .

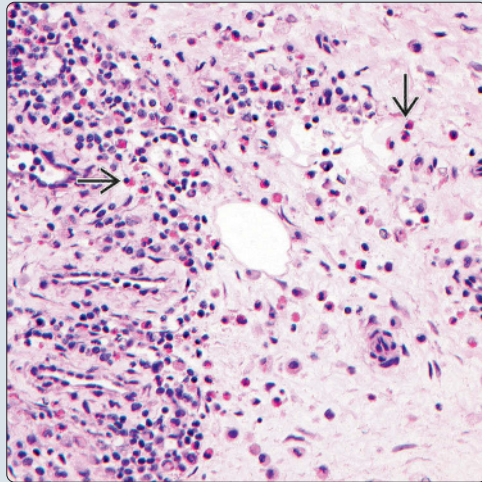


Inflamed Fascia

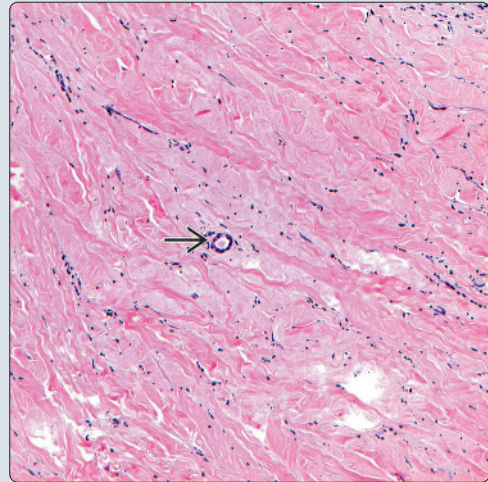


Numerous Eosinophils

(Left) In this portion of the fascia, numerous eosinophils  can be seen along with lymphocytes and plasma cells. Eosinophils can be identified due to their bright red cytoplasmic granules. (Right) Sclerosis of the deep dermis leads to subsequent atrophy of the cutaneous appendages like eccrine glands .



Dermal Sclerosis With Gland Atrophy



## TERMINOLOGY

### Abbreviations

- Eosinophilic fasciitis (EF)

### Synonyms

- Shulman syndrome, diffuse fasciitis with eosinophilia

### Definitions

- Scleroderma-like disorder with symmetric thickening of fascia accompanied by mixed inflammatory infiltrate
  - Induration of skin and soft tissues
  - Unilateral and more localized cases have been reported

## CLINICAL ISSUES

### Epidemiology

- Age
  - Predominantly 2nd-6th decades
- Sex
  - More common in women
- Ethnicity
  - No predilection

### Presentation

- Depressed patches may exhibit groove sign
  - Indentation along longitudinal aspect of superficial vein
- May be associated with
  - Malignancy
    - May precede onset or relapse of cutaneous T-cell lymphoma
  - *Borrelia burgdorferi*
  - Medications
  - Arthropod bites
  - Vigorous exercise
- 30% of cases have comorbid morphea

### Laboratory Tests

- Peripheral eosinophilia
- Elevated erythrocyte sedimentation rate
- Hypergammaglobulinemia
- Antinuclear antibody positivity
- Increased circulating immune complexes

### Treatment

- Drugs
  - Corticosteroids, cyclosporine A, methotrexate, cyclophosphamide
  - Infliximab, etanercept, intravenous immune globulin
  - Dapsone, D-penicillamine, azathioprine, retinoids
- Light
  - Psoralen and ultraviolet A

### Prognosis

- Convalescence typically within 5 years
  - May follow treatment, may be spontaneous
  - May progress to scleroderma

## IMAGING

### MR Findings

- Thickening of muscular fascia with T2-weighted images

- Increased enhancement of affected fascia &/or tendon sheath after contrast agent injection with T1 images

### Positron Emission Tomography

- Increased FDG within involved fascia

## MICROSCOPIC

### Histologic Features

- Fascia edema and thickening
- Infiltrate of eosinophils, lymphocytes, histiocytes, and plasma cells
  - Eosinophils may be focal or prominent
- Thickening of adipose tissue and interlobular fascia
- Sclerosis of deep dermis
  - Atrophy of cutaneous appendages
- Septal thickening may extend into skeletal muscle

## ANCILLARY TESTS

### Immunofluorescence

- May have immunoglobulins and C3 in vessel walls

## DIFFERENTIAL DIAGNOSIS

### Scleroderma

- Thickening of fascia and septa with sparse or absent inflammation
- Raynaud phenomenon, visceral involvement

### Linear Scleroderma

- Distribution along Blaschko lines
- Skin atrophy
- Dermal fibrosis
- Loss of scalp hair &/or eyelashes
- Onset in childhood

### Morphea Profunda (Subcutaneous Morphea)

- Localized indurated plaques
- Thickening and hyalinization of fascia and adipose tissue septa
- Mixed inflammatory infiltrate with multinucleated giant cells

### Eosinophilic Myositis/Perimyositis

- Associated with *Sarcocystis* species, some medications
- May be seen in setting of polymyositis, Churg-Strauss syndrome, or other systemic diseases
- Limited to muscle compartments
- Thickening of septa in skeletal muscle with mixed inflammatory infiltrate
- Peripheral eosinophilia

### Eosinophilia-Myalgia Syndrome

- Associated with ingestion of L-tryptophan
- Myalgias precede peripheral eosinophilia
- May have arthralgias, neuropathy, alopecia, &/or skin thickening

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## KEY FACTS

### TERMINOLOGY

- Synonyms
  - Pseudosarcomatous fasciitis, subcutaneous pseudosarcomatous fibromatosis

### CLINICAL ISSUES


- Presentation
  - Benign, rapidly growing soft tissue mass
- Treatment/prognosis
  - Simple excision is typically curative
  - Most lesions do not recur, even if incompletely excised
- Pseudomalignancy
  - Cannot rely on clinical or frozen tissue for decision on how aggressive surgery should be
  - Easy to overtreat with overzealous surgery

### MICROSCOPIC

- Loose, feathery pattern with variable myxoid stroma, cystic spaces, strands of keloid-like collagen

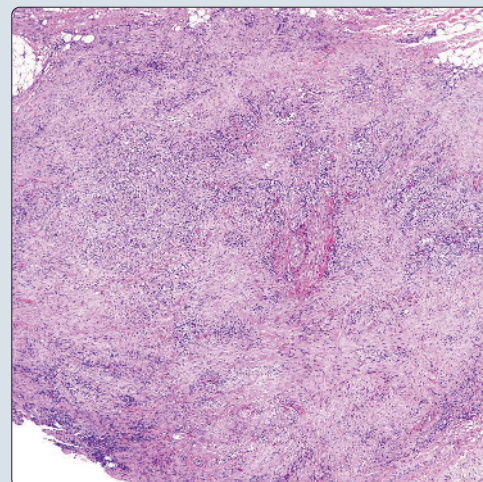
- Tissue paper or cell culture appearance
- Myofibroblastic proliferation with storiform pattern
  - Actin-sm (+), desmin variably positive
- Mitoses present, but no atypical forms
- Extravasated erythrocytes without associated hemosiderin
- 3 forms reported: Myxoid, cellular, and fibrous
  - Loose correlation with duration of lesions
  - Myxoid lesion often resected within 10 days after coming to clinical attention
  - Cellular and fibrous forms resected after longer intervals
- Variants
  - Nodular myositis
  - Intravascular fasciitis
  - Cranial fasciitis
  - Proliferative fasciitis
  - Intradermal nodular fasciitis

Subcutaneous Nodule Clinically



(Left) Nodular fasciitis (NF) clinically presents as a subcutaneous nodule , typically on the upper extremity (forearm especially) of young adults. (Courtesy J. W. Steger, MD.) (Right) At low magnification, NF presents as a moderately well-circumscribed nodule reminiscent of granulation tissue in the subcutaneous tissue.

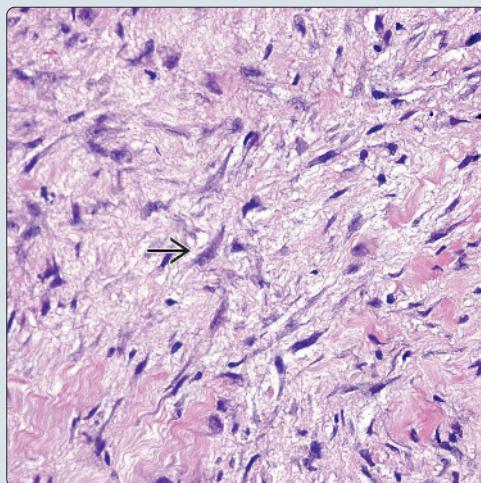


Nodule Within Subcutis

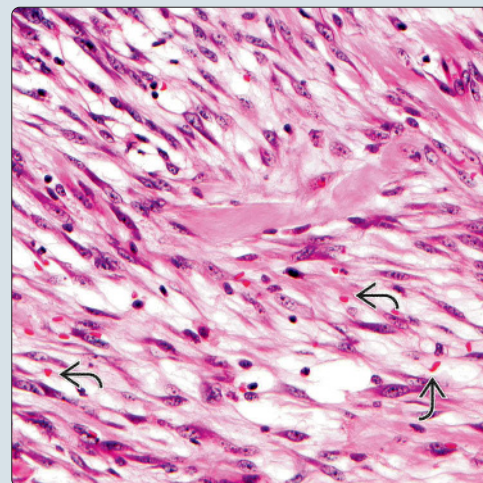


Stellate Cells

(Left) This lesion displays stellate cells and thickened collagen bundles. The nuclei are pale with delicate small nucleoli . (Right) High-power view of NF shows extravasated red blood cells  without hemosiderin and with loosely arranged whorls of elongated, spindled, fibroblast-like cells imparting a storiform pattern. (Courtesy S. de Feraudy, MD.)



Loose Configuration With Red Blood Cells



## TERMINOLOGY

### Abbreviations

- Nodular fasciitis (NF)

### Synonyms

- Pseudosarcomatous fasciitis, subcutaneous pseudosarcomatous fibromatosis

### Definitions

- Benign, rapidly growing myofibroblastic proliferation
  - Cellular and mitotically active

## ETIOLOGY/PATHOGENESIS

### Unknown

- Often history of trauma

## CLINICAL ISSUES

### Presentation

- Typically presents as subcutaneous mass in upper extremities, trunk, and head and neck in young adults
- Lesion usually rapidly growing and painless

### Treatment

- Surgical approaches
  - Excision usually curative
- Adjuvant therapy
  - Intralesional corticosteroids can also be used

## MACROSCOPIC

### General Features

- Well demarcated but unencapsulated
- Variable mucoid appearance

## MICROSCOPIC

### Histologic Features

- Myofibroblastic proliferation with storiform pattern
- Loose, feathery pattern with variable myxoid stroma, cystic spaces, and strands of keloid-like collagen
  - Tissue paper or cell culture appearance
- Mitoses present but no atypical forms
- Osteoclast-like giant cells found in most lesions if sought
- Scattered lymphocytes and essentially no plasma cells
- Extravasated erythrocytes without associated hemosiderin
- 3 forms reported: Myxoid, cellular, and fibrous
  - Loose correlation with duration of lesions
    - Myxoid lesion often resected within 10 days after coming to clinical attention
    - Cellular and fibrous forms resected after longer intervals
    - Some lesions show several patterns

### Variants

- Nodular myositis
  - Same as NF but intramuscular
- Intravascular fasciitis
  - Arises in lumen of small or medium-sized vessels
  - Typically displays abundant osteoclast-like giant cells
- Cranial fasciitis

- Erodes into bone and may penetrate through to involve meninges
- Proliferative fasciitis
  - Large cells with abundant eosinophilic cytoplasm which resemble ganglion cells
- Intradermal NF
  - Morphologic features are similar to ordinary NF

## ANCILLARY TESTS

### Cytology

- Shows myofibroblastic cells
  - Lesions are cellular, which can lead to erroneous impression of sarcoma on aspiration cytology

## DIFFERENTIAL DIAGNOSIS

### Fibrous Histiocytoma (Dermatofibroma)

- Collagen trapping at periphery of lesions
- May have foamy macrophages, hemosiderin, &/or plasma cells
- FXIIIa(+), CD34(-), variable actin-sm reactivity

### Dermatofibrosarcoma Protuberans

- Storiform pattern involving deep dermis and subcutis
  - Entrapping adipose tissue
- CD34(+), FXIIIa(-), negative for muscle markers

### Neurofibroma

- Wavy nuclei with interspersed shredded carrot-like collagen
- Increase in mast cells
- S100 protein reactive, variable CD34(+) supporting cells

### Fibromatosis

- Large, deep, infiltrative lesions
  - Shoulder girdle is common site
  - Abdominal wall in women in reproductive years (desmoid tumor)
- Sweeping fascicles of myofibroblasts with dense collagen deposition
- No atypia or mitoses
- Actin-sm (+), nuclear  $\beta$ -catenin (+)

### Kaposi Sarcoma

- Found in immunocompromised patients (especially AIDS patients)
- Spindled cells with slit-like vascular spaces
- Extravasated erythrocytes, hemosiderin, plasma cells, hyaline globules
- CD34, CD31, and HHV8 (+)

### Leiomyosarcoma

- Fascicles of eosinophilic smooth muscle cells
- Mitoses invariably increased  $\pm$  cellular atypia and necrosis
- Actin-sm, desmin, calponin, and caldesmon positive

## SELECTED REFERENCES

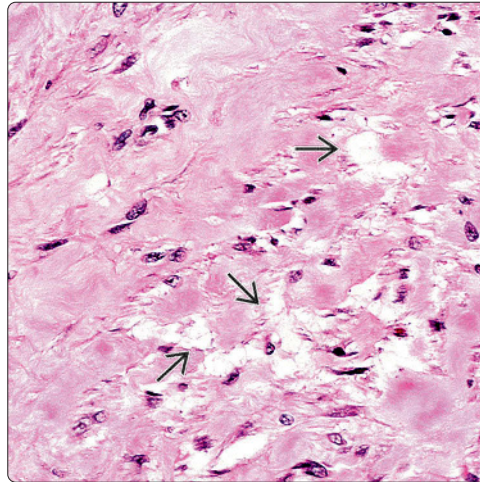
1. Hourani R et al: Fibroblastic and myofibroblastic tumors of the head and neck: comprehensive imaging-based review with pathologic correlation. *Eur J Radiol.* 84(2):250-60, 2015
2. Lu L et al: Nodular fasciitis: a retrospective study of 272 cases from China with clinicopathologic and radiologic correlation. *Ann Diagn Pathol.* ePub, 2015



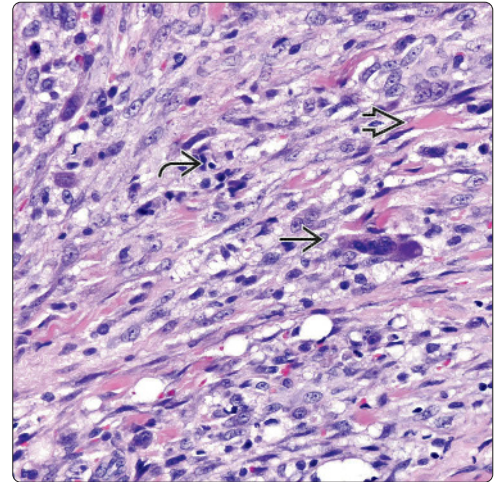
## Nodular Fasciitis

Tissue Paper Appearance

(Left) NF with keloid-like collagen can be misinterpreted, especially in core biopsy, as a fibromatosis. The cells appear torn apart [2]. This characteristic finding is due to mucin deposits and is referred to as tissue paper or cell culture appearance. (Right) The nuclei in NF are bland and uniform. This field shows an osteoclast-like giant cell [2] and strands of dense collagen [2]. There are scattered background lymphocytes [2] that appear more hyperchromatic than the proliferating cells.

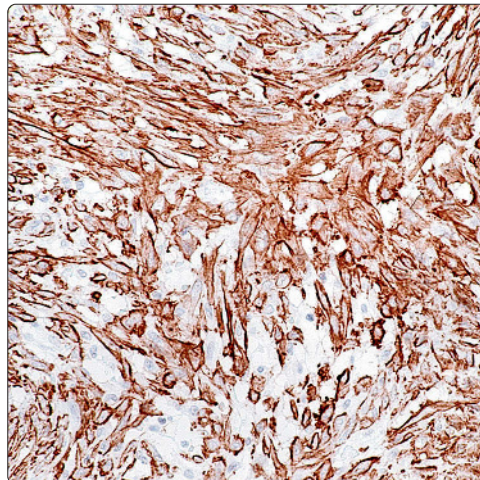


Giant Cells

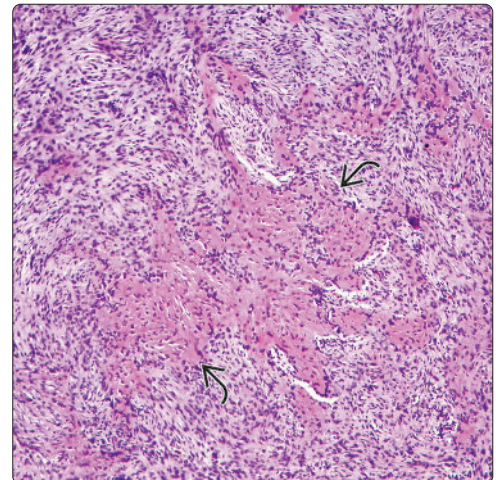


Smooth Muscle Actin Positivity

(Left) Actin-sm highlights the stellate proliferating myofibroblasts. This feature of NF can lead to a misinterpretation of leiomyosarcoma since mitoses are often found in NF. However, peripheral localization of staining within the cells is characteristic of myofibroblasts. (Right) Occasionally, NF can demonstrate osteoid formation [2] and a more typical surrounding myofibroblastic proliferation of spindled cells. (Courtesy S. de Feraudy, MD.)

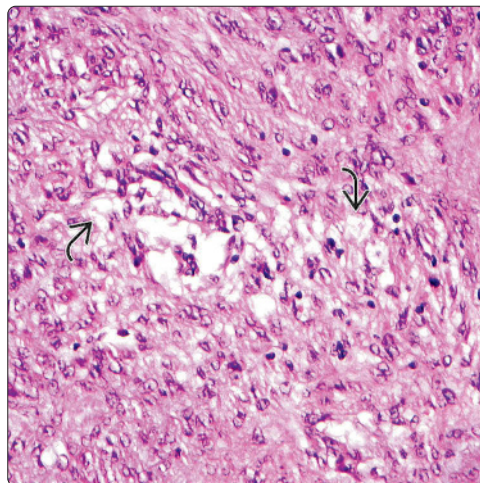


Nodular Fasciitis With Osteoid

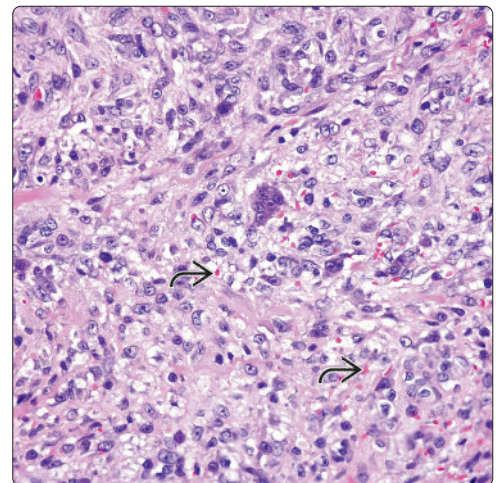


Microcystic Change in Nodular Fasciitis

(Left) Intradermal NF can show characteristic changes found in ordinary NF, such as microcystic formation [2]. (Courtesy S. de Feraudy, MD.) (Right) Each myofibroblast contains a uniform nucleolus. Scattered extravasated erythrocytes are present without accompanying hemosiderin [2].

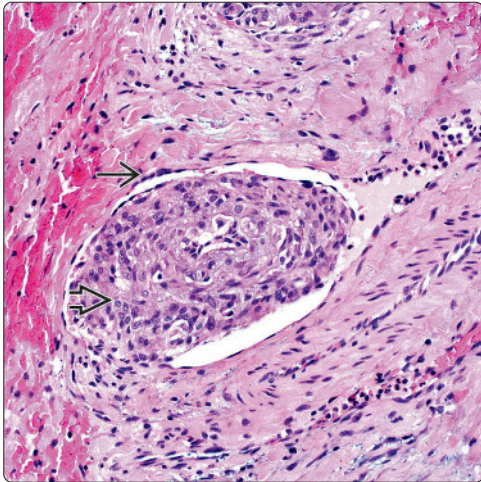


Nucleoli and Red Blood Cells

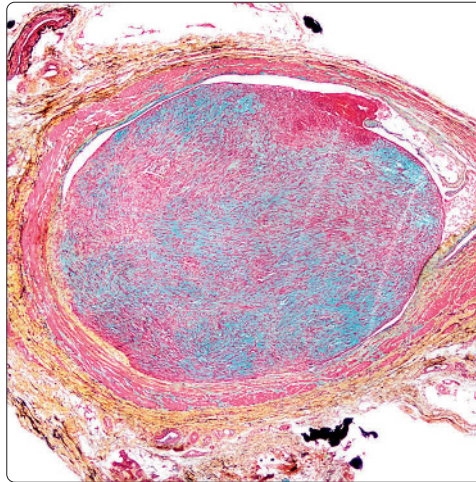




**Intravascular Fasciitis**

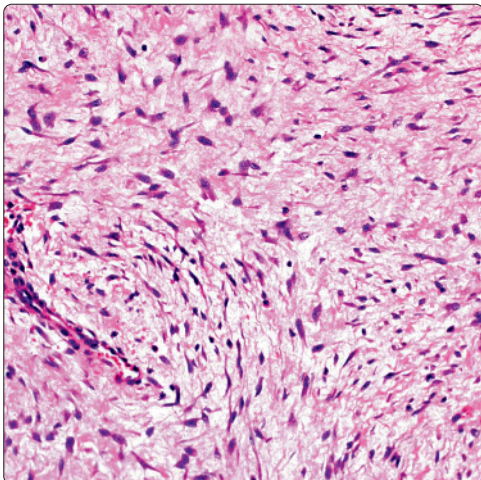


**Trichrome Stain of Intravascular Fasciitis**

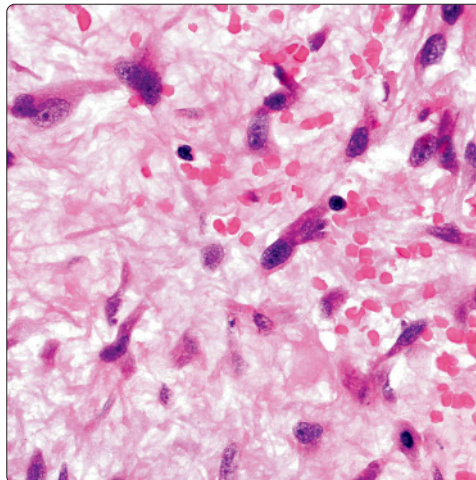


(Left) Intravascular fasciitis is a subtype that may involve all types of vessels, including a small capillary. In this image, the lesional cells   have much paler nuclei than the surrounding endothelial cells  . (Right) A trichrome stain shows intravascular NF that nearly occludes the vessel. Surprisingly, this does not usually result in any functional impairment, but the patient typically complains of a mass. Veins or arteries can be involved and the lesional tissue sometimes extends through the vessel wall.

**Cranial Fasciitis**

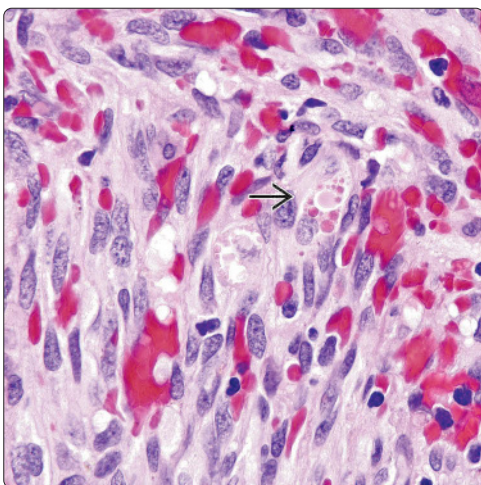


**Cranial Fasciitis Nuclear Features**

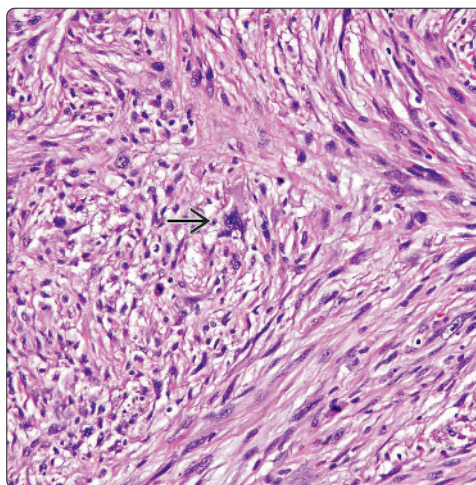


(Left) This is an example of cranial fasciitis. At low magnification, the lesion appears loose, myxoid, and uniform. There are fewer inflammatory cells and extravasated erythrocytes than typical NF. (Right) The proliferating myofibroblasts of cranial fasciitis have similar nuclear features to those of typical NF and intravascular fasciitis.

**Kaposi Sarcoma With Hyaline Globules**



**Pleomorphic Undifferentiated Sarcoma, Pleomorphic Nuclei**



(Left) H&E of Kaposi sarcoma shows hyperchromatic lesional cells and hyaline globules  . The latter are erythrophagolysosomes. (Right) H&E stain shows a malignant fibrous histiocytoma (pleomorphic undifferentiated sarcoma). Note the storiform pattern and markedly pleomorphic nuclei  .



## KEY FACTS

### TERMINOLOGY

- Inherited disorder characterized by fragmentation and progressive calcification of elastic tissue in dermis, blood vessels, and Bruch membrane of eye

### CLINICAL ISSUES

- Predilection for flexural creases
  - Sides of neck
  - Axillae, groins, periumbilical, antecubital, and popliteal fossae
- Cutaneous manifestations
  - Highly characteristic
  - Small, yellow papules of 1-5 mm in diameter in linear or reticular pattern
  - Coalescence in plaques with cobblestone appearance
  - Soft, lax and wrinkled skin, hanging in folds, resembling cutis laxa

### MICROSCOPIC

- Elastic fibers are fragmented, swollen, and clumped in middle and deep reticular dermis
- Positive stain for elastic fibers (Verhoeff-van Gieson) and calcium deposition (von Kossa)

### TOP DIFFERENTIAL DIAGNOSES

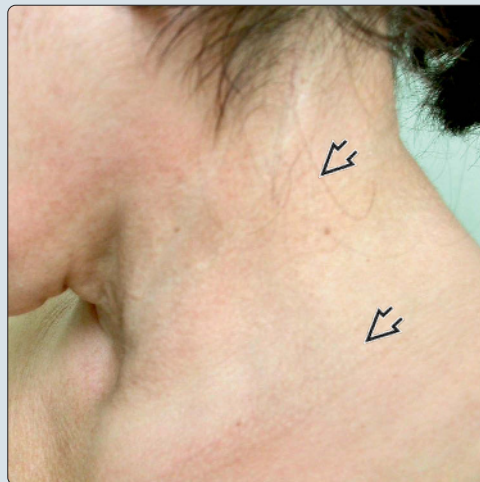
- Acquired pseudoxanthoma elasticum (PXE)-like syndromes

### DIAGNOSTIC CHECKLIST

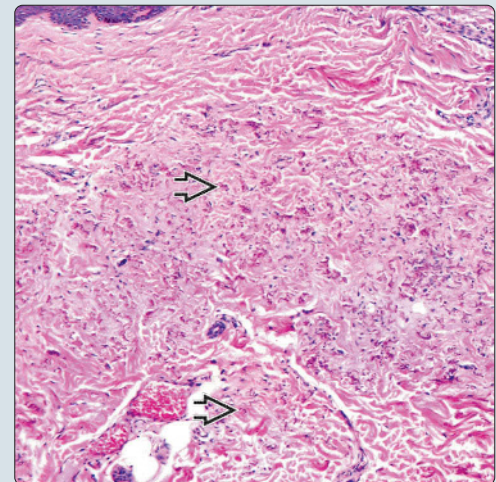
- Major criteria
  - Flexural yellow cobblestone lesions
  - Characteristic histological features of lesional skin
  - Angioid streaks in retina
- Minor criteria
  - Characteristic histological changes in nonlesional skin
  - Family history of PXE in 1st-degree relatives

### Plucked-Chicken Clinical Appearance on Lateral Neck

**(Left)** Clinical photograph shows a slightly pebbly surface of the lateral aspect of the neck with a plucked-chicken appearance in this 30-year-old woman with pseudoxanthoma elasticum (PXE). **(Right)** Basophilic granular material amidst collagen fibers in the middle and deep reticular dermis represents degenerative changes affecting the elastic fibers in PXE.

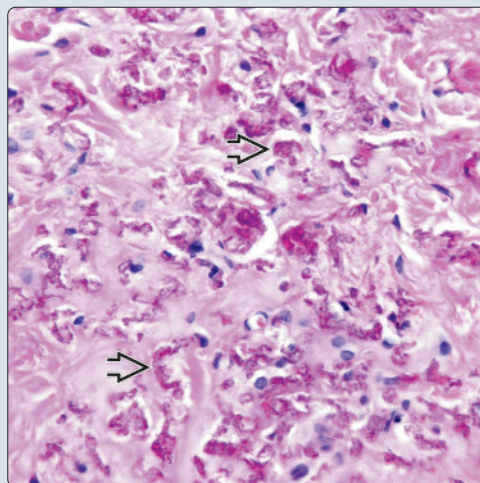


### Basophilic Granular Material in Dermis

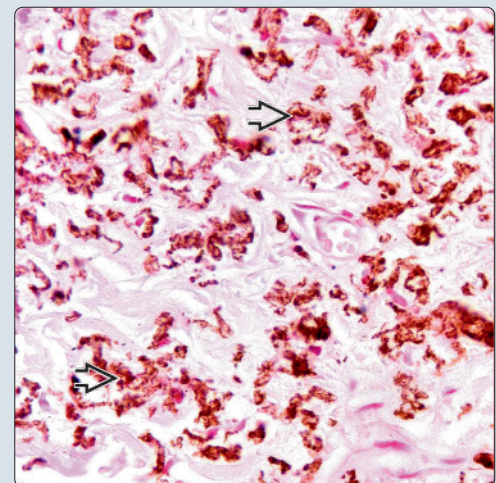


### Fragmented, Clumped Elastic Fibers

**(Left)** Fragmented, swollen, clumped, and basophilic elastic fibers are typical histological changes encountered in PXE. Basophilic appearance on H&E is due to calcium deposition. **(Right)** Calcium deposition within elastic fibers in PXE is highlighted by von Kossa stain.



### Calcium Deposition in Elastic Fibers With von Kossa Stain



## TERMINOLOGY

### Abbreviations

- Pseudoxanthoma elasticum (PXE)

### Synonyms

- Systematized elastorrhexis; Grönblad-Strandberg syndrome

### Definitions

- Inherited disorder characterized by fragmentation and progressive calcification of elastic tissue in dermis, blood vessels, and Bruch membrane of eye

## ETIOLOGY/PATHOGENESIS

### Etiology

- Mutations in *ABCC6* gene, mapped on 16p13.1
- Encodes cellular transport protein ABCC6/MRP6 (multidrug resistance-associated protein 6)
- Autosomal recessive mode of inheritance

### Pathogenesis

- Currently thought to represent systemic metabolic disorder with secondary mineralization of connective tissues

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - 1:70,000 to 1:100,000
- Age
  - Usually onset in childhood or early adolescence
- Sex
  - F:M ratio = 2:1
- Ethnicity
  - All races may be affected

### Site

- Predilection for flexural creases
  - Sides of neck
  - Axillae, groins, periumbilical, antecubital, and popliteal fossae
- Buccal, vaginal, and rectal mucosa

### Presentation

- Cutaneous manifestations
  - Highly characteristic
  - Small, yellow papules of 1-5 mm in diameter in linear or reticular pattern
  - Coalescence in plaques with cobblestone appearance
  - Soft, lax and wrinkled skin, hanging in folds, resembling cutis laxa
- Ocular manifestations
  - Retinal angioid streaks
    - Highly characteristic, but not pathognomonic
    - Represent cracks and fissures in Bruch membrane
    - Gray to reddish brown, jagged radiating bands in perimacular region of retina
- Cardiovascular manifestations
  - Increased blood vessel fragility due to calcification of elastic media and intima
    - Angiomatous malformations, aneurysmal dilatation

- Narrowing/occlusion of peripheral and visceral arteries

- Mitral valve prolapse

### Treatment

- Options, risks, complications
  - Progressive loss of central vision due to retinal hemorrhage
  - Claudication, hypertension, angina, and myocardial infarction
  - GI, urinary, and cerebral hemorrhage
- Surgical approaches
  - Laser photocoagulation prevents retinal hemorrhage
- Adjuvant therapy
  - Control of blood pressure and serum lipids
  - Avoidance of aspirin, NSAIDs, and anticoagulants
  - Avoidance of smoking
- Drugs
  - Hemorheologic agents such as pentoxifylline used for symptomatic treatment of peripheral vascular disease
  - Vitamin A, C, and E, and zinc supplements may be beneficial

### Prognosis

- Usually normal life span
- Myocardial infarction, GI or cerebral hemorrhage may be fatal

## MICROSCOPIC

### Histologic Features

- Fragmented, swollen, and clumped elastic fibers in middle and deep reticular dermis
- Basophilic appearance on H&E due to calcium deposition
- Similar changes in connective tissue of blood vessels, Bruch membranes, endocardium, and pericardium
- Positive stain for elastic fibers (Verhoeff-van Gieson) and calcium deposition (von Kossa)

## DIFFERENTIAL DIAGNOSIS

### Acquired Pseudoxanthoma Elasticum-Like Syndromes

- Perforating PXE, pseudoPXE due to penicillamine, saltpeter disease, Williams-Beuren syndrome, PXE-like papillary dermal elastolysis, linear focal elastolysis, and late-onset dermal elastosis

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Flexural yellow cobblestone lesions
- Retinal angioid streaks

### Pathologic Interpretation Pearls

- Fragmented, swollen, and clumped elastic fibers in mid and deep reticular dermis

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1. Aung PP et al: Pseudoxanthoma elasticum-like change adjacent to a benign adnexal neoplasm: a histopathologic reaction pattern. *Am J Dermatopathol*. 37(2):157-9, 2015
2. el-Charif MA et al: Pseudoxanthoma elasticum-like papillary dermal elastolysis: a report of two cases. *J Cutan Pathol*. 21(3):252-5, 1994



## Relapsing Polychondritis

## KEY FACTS

## TERMINOLOGY

- Chronic multisystem disease characterized by remitting and relapsing inflammation and destruction of cartilaginous and other proteoglycan-rich tissue

## CLINICAL ISSUES

- Auricular chondritis: Cauliflower ear
- Arthritis: Migratory, nonerosive
- Nasal chondritis: Saddle nose deformity
- Diagnostic criteria (3 of 6 required)
  - Bilateral auricular chondritis
  - Nonerosive inflammatory polyarthritis
  - Nasal chondritis
  - Ocular inflammation
  - Respiratory tract chondritis
  - Audiovestibular damage
- Life threatening: Respiratory collapse, infection, systemic vasculitis, renal failure

## MICROSCOPIC

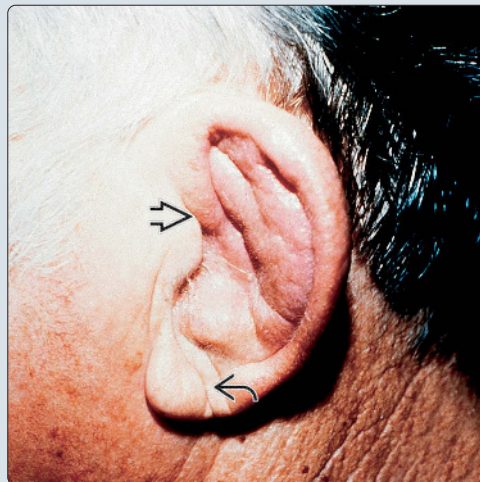
- Early: Loss of chondrocyte basophilia, perichondritis
- Late: Granulation tissue and fibrosis

## TOP DIFFERENTIAL DIAGNOSES

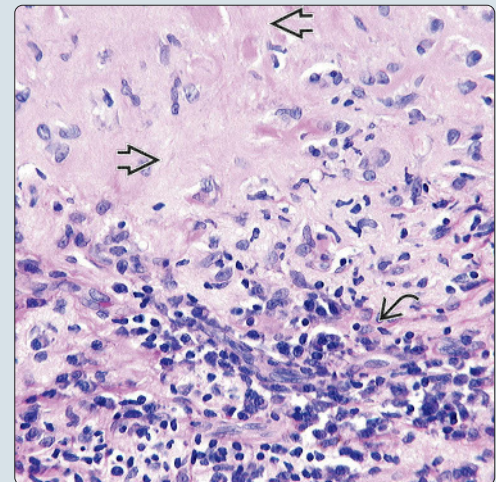
- Granulomatosis with polyangiitis (Wegener)
  - Histologic: Granulomatous vasculitis
  - Laboratory: Antibodies to c-ANCA
- Leprosy
  - Clinical: Saddle nose deformity; earlobes affected; leonine facies; numerous ill-defined, symmetrically distributed, erythematous to hypopigmented papules, nodules, plaques
  - Histologic: Diffuse dermal infiltrate of foamy histiocytes; grenz zone; numerous AFB(+) organisms

Cauliflower Ear of Relapsing Polychondritis

(Left) Relapsing polychondritis (RPC) shows chronic inflammation/destruction limited to the cartilaginous ear that has led to the formation of cauliflower ear. The earlobe is spared. (Courtesy L. Thompson, MD.) (Right) Late RPC chondritis shows loss of chondrocyte matrix basophilia (eosinophilic matrix change), loss of lacunar outline/chondrocytes, and lymphocytic perichondritis.



Loss of Chondrocyte Matrix and Lymphocytic Perichondritis

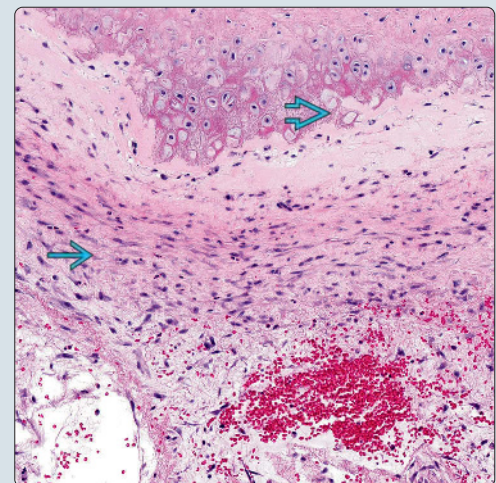


Saddle Nose Deformity of Relapsing Polychondritis

(Left) Saddle nose deformity may be seen in RPC, Wegener granulomatosis, and lepromatous leprosy. (Courtesy of the Victor D. Newcomer Collection at UCLA.) (Right) High-power H&E of RPC demonstrating perichondrial fibrosis and vacuolization of the remaining basophilic chondrocytes.



Perichondrial Fibrosis and Vacuolization of Chondrocytes



## TERMINOLOGY

### Abbreviations

- Relapsing polychondritis (RPC)

### Synonyms

- Polychondroplasia, chondromalacia, chronic atrophic polychondritis

### Definitions

- Chronic multisystem disease characterized by remitting/relapsing inflammation/destruction of cartilaginous and other proteoglycan-rich tissue

## ETIOLOGY/PATHOGENESIS

### At Least Partially Autoimmune

- Unspecified insult exposes epitopes, genetically primed immune response to cartilaginous tissues
  - Humoral and cellular immunity involved
  - Matrilin-1: Cartilage matrix protein, potential autoantigen

### Genetic Component

- Associated with HLA-DR4, HLA-DR6

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Rare; ~ 3 cases per 1 million
- Age
  - Most commonly adults; peak onset: 40-50 years

### Site

- Multisystem disease: Bilateral auricles (89%), joints (81%), nasal (72%), ocular (65%), respiratory tract (56%), audiovestibular (46%)

### Presentation

- Relapsing episodic inflammation of articular and nonarticular cartilage and other proteoglycan-rich tissue
- ~ 50% present with auricular chondritis &/or arthritis
  - Auricular chondritis
    - Acute: Erythema, edema, and pain limited to cartilaginous ear (earlobe spared)
    - Chronic: Scarring with auricular distortion (cauliflower or floppy ear)
  - Arthritis
    - Parasternal joints: Tenderness, clavicular or rib dislocation, flail chest
    - Peripheral joints: Migratory, nonerosive, inflammatory arthritis with effusions

### Laboratory Tests

- Markers of disease activity: Antitype II collagen antibodies, urinary mucopolysaccharides, serum cartilage oligomeric matrix protein, erythrocyte sedimentation rate

### Prognosis

- Significant morbidity/mortality without treatment

## Disease Associations

- 30% associated systemic disease: Rheumatoid arthritis, lupus erythematosus, Sjögren disease, vasculitis, hematologic disorder
- MAGIC syndrome = mouth and genital ulcers with inflamed cartilage (RPC + Behçet disease)

## Complications

- Nose: Erythema, edema, pain, epistaxis, saddle nose
- Eye: Episcleritis, scleritis
- Pulmonary: Infection, obstruction/collapse
- Audiovestibular: Tinnitus, vertigo, ataxia, hearing loss
- Cardiac: Valvular and conduction defects, aneurysms
- Neurologic: Cranial neuropathies
- Renal: Glomerulonephritis, IgA nephropathy
- Skin: Aphthosis, pustules, vasculitis, panniculitis
- Constitutional symptoms

## MICROSCOPIC

### Histologic Features

- Early lesions: Loss of matrix mucopolysaccharides leading to loss of chondrocyte matrix basophilia, perichondritis ± elastic fiber clumping; neutrophils predominate
- Late lesions: Chondrocyte vacuolization/pyknosis/loss, perichondral granulation tissue/fibrosis ± calcification/ossification; lymphocytes predominate

## ANCILLARY TESTS

### Immunofluorescence

- Granular IgG > IgA, IgM, C3 deposits within cartilage matrix

## DIFFERENTIAL DIAGNOSIS

### Auricular Chondritis

- Pseudocyst of auricle (cystic chondromalacia)
  - Clinical: Unilateral, painless, noninflammatory swelling of upper 1/3 ear
  - Histologic: Intercartilaginous cavity; no epithelial lining
- Bacterial auricular perichondritis
  - Clinical: Often unilateral; ± earlobe sparing
  - Cultures: Positive

### Nasal Chondritis

- Granulomatosis with polyangiitis (Wegener)
  - Clinical: Saddle nose deformity; ear involvement but no auricular chondritis; pulmonary/renal/joint involvement
  - Histologic: Granulomatous vasculitis
  - Laboratory: Antibodies to c-ANCA
- Lepromatous leprosy
  - Clinical: Saddle nose deformity; earlobes affected; leonine facies; numerous ill-defined, symmetrically distributed, erythematous to hypopigmented papules, nodules, plaques
  - Histologic: Diffuse dermal infiltrate of foamy histiocytes; grenz zone; numerous AFB(+) organisms

## SELECTED REFERENCES

1. Longo L et al: Relapsing polychondritis: A clinical update. *Autoimmun Rev*. ePub, 2016



# Nephrogenic Fibrosing Dermopathy (Nephrogenic Systemic Fibrosis)

## KEY FACTS

### TERMINOLOGY

- Scleromyxedema-like dermatosis that affects only patients with renal failure

### ETIOLOGY/PATHOGENESIS

- Gadolinium administration prior to MR imaging
- Gadodiamide (Omniscan) and gadopentetate (Magnevist) specifically
- Have been given to virtually every reported patient prior to disease manifestation
- Have been identified within lesional tissue
- Gadolinium is proposed to upregulate tissue transglutaminases and transforming growth factor- $\beta$  (TGF- $\beta$ ), leading to increased fibrosis

### CLINICAL ISSUES

- History of renal failure is universally present
- Dialysis not required prerequisite

- Thickening and hardening of skin over days, weeks, or months
- Papules and plaques over involved areas

### MICROSCOPIC

- Fibrosis of dermis and subcutaneous septa
- Increased numbers of fibroblasts
- Spindled cells in between collagen fibers
- Haphazard collagen bundles in affected deep dermis and adipose septa
- Increased mucin deposition around fibroblasts
- Increased histiocytes in between collagen bundles

### TOP DIFFERENTIAL DIAGNOSES

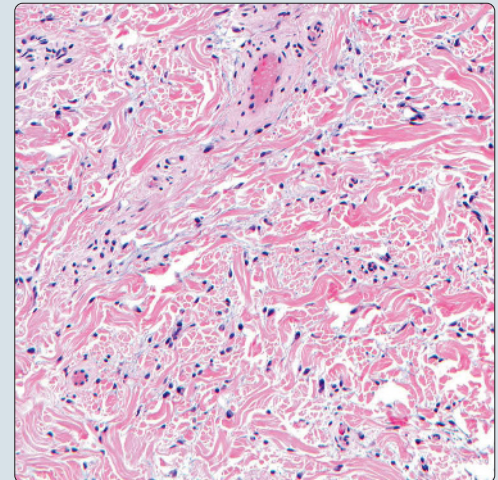
- Scleromyxedema
- Scleroderma
- Pretibial myxedema
- Scleredema (scleredema adutorum of Buschke)
- Reticular erythematous mucinosis

Thickened, Indurated Skin

(Left) This patient is unable to open her hand due to indurated skin. She was given gadolinium contrast months before. The skin is firm but not bound down as in scleroderma. (Right) There is an increased population of spindle-cell histiocytes and fibroblasts with faint gray/blue mucin deposition in between the collagen bundles.

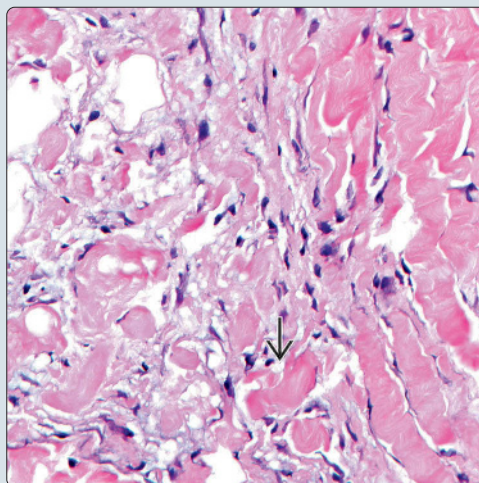


Cellular Dermis

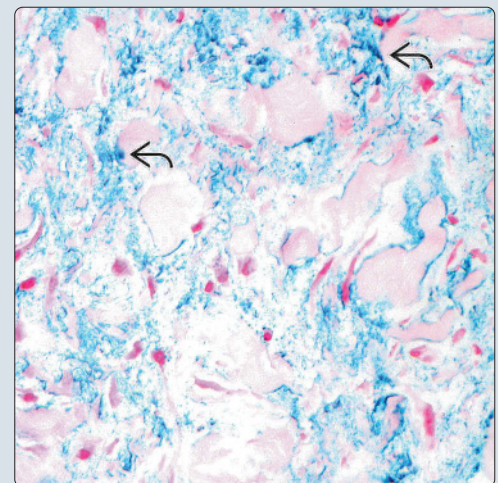


Involvement of Septa

(Left) In this subcutaneous septum there is a haphazard arrangement of collagen bundles with admixed mucin. (Right) The presence of increased mucin (granular blue staining) is confirmed with a Hale colloidal iron stain.



Increased Mucin





## TERMINOLOGY

### Abbreviations

- Nephrogenic fibrosing dermopathy (NFD)

### Synonyms

- Nephrogenic systemic fibrosis (NSF)

### Definitions

- Scleromyxedema-like dermatosis that affects only patients with renal failure

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- Gadolinium administration prior to MR imaging
  - Gadodiamide (Omniscan) and gadopentetate (Magnevist) specifically
    - Have been given to virtually every reported patient prior to disease manifestation
    - Have been identified within lesional tissue
    - Stored in bone and slowly released over time

### Pathogenesis

- Release of gadodiamide has been proposed to lead to upregulation of
  - Tissue transglutaminases
  - Transforming growth factor- $\beta$  (TGF- $\beta$ )
  - These factors act to increase fibrosis
- Fibroblasts cultured from these lesions have increased mucin and hyaluronan production

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Since identification of gadolinium as causative agent, it is extremely rare
- Age
  - Can present at any age
    - Most frequent in older patients (renal failure more common)

### Presentation

- History of renal failure is universally present
  - Dialysis not required prerequisite
- Thickening and hardening of skin over days, weeks, or months
- Papules and plaques over involved areas
  - Usually extremities and trunk
  - Involvement of hands can cause sclerodactyly &/or joint contractures
- $\pm$  muscle weakness, pain, pruritus
- Calcium dysregulation is more commonly reported in these patients
  - Calciophylaxis, calcinosis cutis, and metastatic calcification have all been reported

### Treatment

- Drugs
  - Intravenous immunoglobulins, retinoids
- Light
  - Ultraviolet (UV) A1 phototherapy

- Psoralen and UVA (PUVA)
- Extracorporeal photopheresis

## MICROSCOPIC

### Histologic Features

- Fibrosis of dermis and subcutaneous septa
- Increased numbers of fibroblasts
  - Spindled cells in between collagen fibers
- Haphazard collagen bundles in affected deep dermis and adipose septa
- Increased mucin deposition around fibroblasts
- Increased histiocytes in between collagen bundles
  - Multinucleated giant cells may be seen

## ANCILLARY TESTS

### Histochemistry

- Hale colloidal iron
  - Stains mucin blue

## DIFFERENTIAL DIAGNOSIS

### Clinical and Histopathological

- Scleromyxedema
  - Fibrosis and increased mucin deposition
    - More prominent in upper and mid dermis
  - Does not usually extend into subcutaneous septa
  - Clusters of plasma cells may be seen
- Scleroderma
  - Increased fibrosis of dermis
  - No appreciable increase in mucin
- Pretibial myxedema
  - Concomitant hyperthyroidism
  - Abundant mucin deposition in mid and deep dermis
  - No increase in fibrosis or fibroblasts
- Scleredema (scleredema adutorum of Buschke)
  - Sometimes associated with preceding febrile illness
  - Swollen collagen bundles that are separated from each other
    - Mucin accumulated around collagen bundles
  - No increase in fibroblasts
- Reticular erythematous mucinosis
  - Erythematous macules, papules, and plaques
    - May have reticulated pattern
    - Primarily on chest, back, and abdomen
  - Mild superficial perivascular infiltrate
    - Lymphocytes, mast cells, histiocytes, and dendrocytes
  - Increased mucin in upper and mid dermis
    - Most prominent around chronic inflammatory cells and cutaneous adnexa

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## KEY FACTS

### TERMINOLOGY

- Benign, rare, yet distinctive, atrophic dermal process of uncertain etiology
- Regarded by some as abortive variant of morphea

### CLINICAL ISSUES

- Sharply circumscribed, round to oval, gray-brown-blue or purple, hyperpigmented, atrophic, depressed macule or patch with cliff drop border
  - Also described as footprints in snow from oval shape of depressed lesions
- Trunk (specifically lower back), lower extremities (62.5%) most common; upper extremities and trunk less common

### MICROSCOPIC

- Histopathologic features are subtle
- Normal or atrophic epidermis with hyperpigmented basal layer

- When compared to normal skin, dermal thickness is decreased (very subtle)
- Perivascular and interstitial chronic lymphohistiocytic inflammatory cell infiltrate, with rare plasma cells
- Early lesions have homogenized/hyalinized and swollen collagen bundles; eventually sclerosis predominates in reticular dermis
- Pilosebaceous structures and sweat glands are retained
- Elastic fibers are usually normal but are rarely decreased in density, clumped or fragmented (usually in deeper dermis)
- Late stage is often indistinguishable from localized scleroderma/morphea

### TOP DIFFERENTIAL DIAGNOSES

- Localized scleroderma/morphea
- Atrophoderma elastolytica discreta
- Lichen sclerosus et atrophicus
- Resolving panniculitis

Sharply Demarcated Patch With Cliff Drop Border



Sharply demarcated  areas where the skin seems to drop off a cliff into an area of increased pigment on the abdomen are shown. The skin has no excoriations and is of normal texture.

## TERMINOLOGY

### Synonyms

- Atrophoderma of Pasini and Pierini (APP)

### Definitions

- Benign, rare, yet distinctive, atrophic dermal process of uncertain etiology
- Regarded by some as abortive variant of morphea
  - Ackerman believes it is morphea

## ETIOLOGY/PATHOGENESIS

### Origin

- 1st described by Pasini in 1923 as "progressive idiopathic atrophoderma"
- In 1936, in Argentina, Pierini and Vivoli studied and defined condition and its possible link to morphea
- In 1958, Canizares reviewed Pierini's findings and renamed it idiopathic APP
  - Canizares believed that idiopathic APP differed sufficiently from morphea to classify it as distinct entity
- In 2000, Yokoyama reported that skin glycosaminoglycans extracted from idiopathic APP lesions are distinct from those in typical morphea lesions
- Etiology and pathogenesis remain unknown

### Etiology

- Controversy exists as to whether it represents distinct entity or whether it is variant of localized scleroderma (morphea)
- Congenital variant has been described
- It has been suggested that macrophages and T cells that are present around dermal blood vessels may participate in pathogenesis

## CLINICAL ISSUES

### Epidemiology

- Age
  - 2nd or 3rd decade (mean age: 30 years); onset often around adolescence
    - Has been reported in individuals as young as 7 years and as old as 66 years
- Sex
  - F > M (5:1)

### Site

- Trunk (specifically lower back), lower extremities (62.5%) most common; upper extremities and trunk less common
  - Rarely on chest, arms, and abdomen

### Presentation

- Sharply circumscribed, round to oval, gray-brown-blue or purple, hyperpigmented, atrophic, depressed macule or patch with cliff drop border
  - Also described as footprints in snow from oval shape of depressed lesions
  - Some of clinical appearance can be attributed to optical illusion created by color change
  - Lesions lack induration or wrinkling and can be hypopigmented
  - May be > 20 cm in diameter

- Bilateral and symmetric
  - Widespread unilateral involvement is rare
- Case with zosteriform distribution has been documented
- May coexist with lichen sclerosus and morphea and progression to systemic sclerosis has been reported
- Lesions are often chronic, progressing over many years
- Linear atrophoderma of Moulin: Related condition that follows lines of Blaschko

### Treatment

- No definitively effective treatment is currently available

### Prognosis

- Benign and not reportedly associated with any significant complications or mortality

## MICROSCOPIC

### Histologic Features

- Histopathologic features are subtle
- Normal or atrophic epidermis with hyperpigmented basal layer
  - It is often helpful to have normal skin adjacent to abnormal skin, as changes can be extremely subtle
- When compared to normal skin, dermal thickness is decreased (very subtle)
- Perivascular and interstitial chronic lymphohistiocytic inflammatory cell infiltrate, with rare plasma cells
- Early lesions have homogenized/hyalinized and swollen collagen bundles; eventually sclerosis predominates in reticular dermis
- Pilosebaceous structures and sweat glands are retained
- Elastic fibers are usually normal but are rarely decreased in density, clumped or fragmented (usually in deeper dermis)
- Late stage is often indistinguishable from localized scleroderma/morphea

## DIFFERENTIAL DIAGNOSIS

### Localized Scleroderma/Morphea

- In contrast to localized scleroderma/morphea, atrophoderma lacks violet border, is primarily atrophic rather than indurated, and tends to have chronic course; morphea tends to resolve after several years

### Atrophoderma Elastolytica Discreta

- Clinically simulates APP
- Histopathology is that of anetoderma

### Lichen Sclerosus et Atrophicus

- Lack pigmentation seen with idiopathic APP

### Resolving Panniculitis

- Lack pigmentation seen with idiopathic APP

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# Favre-Racouchot Syndrome

## KEY FACTS

### TERMINOLOGY

- Also called nodular cutaneous elastosis with cysts and comedones

### ETIOLOGY/PATHOGENESIS

- Exact mechanism unknown, but thought to be due to chronic sun exposure
- Heavy smoking is often implicated

### CLINICAL ISSUES

- Presents as multiple open and closed comedones and cystic nodules on background of heavily sun-damaged skin
- Favors lateral and inferior aspects of the periorbital area
- Favre-Racouchot syndrome (FRS) is benign, but cosmetically displeasing

### MICROSCOPIC

- Dilated pilosebaceous openings and cyst-like spaces filled with horny material

- Often in association with of solar elastosis and epidermal atrophy
- May be colonized with bacteria and *Malassezia* yeast
  - Bacteria include *Propionibacterium acnes*, *Corynebacterium* spp.

### TOP DIFFERENTIAL DIAGNOSES

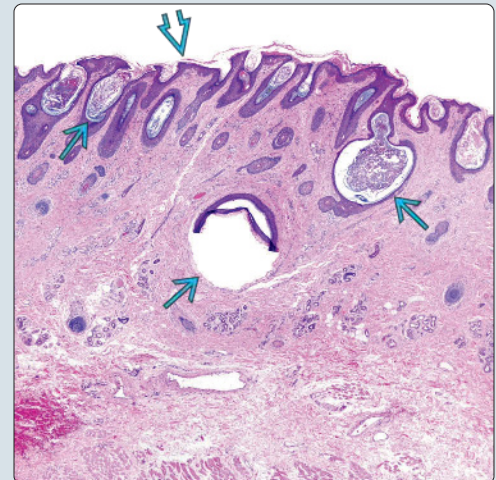
- Histopathologic
  - Primary comedones of acne vulgaris
    - Indistinguishable histopathologically
      - However, inflammation is conspicuously absent in FRS
    - Surrounding skin of FRS shows marked solar elastosis
  - Nodular solar elastosis
    - Lacks multiple comedones and cysts of FRS
- Clinical
  - Chloracne
  - Milia
  - Colloid milium

Open and Closed Comedones

(Left) Photograph shows mainly open comedones and a few closed comedones on the face of an elderly fair-skinned man who had severe solar damage. The temples and periorcular areas are the most common locations for Favre-Racouchot. (Right) Numerous comedones and cysts are present [2]. Epidermal atrophy, typical of sun-damaged skin, is also present [3].

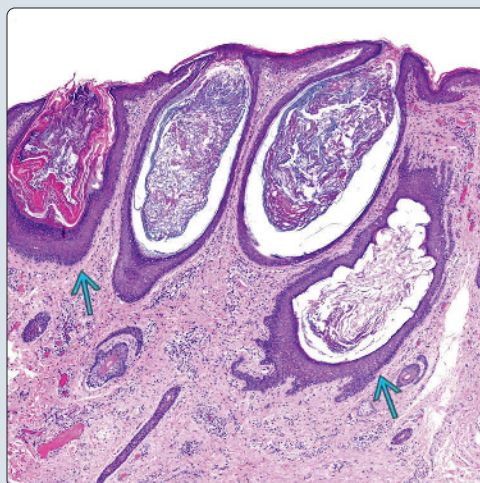


Numerous Comedones and Cysts

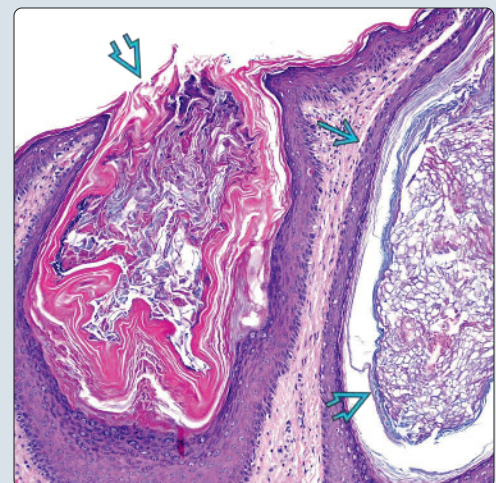


Dilated Pilosebaceous Units

(Left) Dilated pilosebaceous units filled with layered horny material are present [2]. Note the paucity of inflammation. (Right) Comedones and cysts are lined by flattened epithelium [2] and filled with layered horny material [3].



Comedones and Cysts Filled With Horny Material



## TERMINOLOGY

### Abbreviations

- Favre-Racouchot Syndrome (FRS)

### Synonyms

- Nodular cutaneous elastosis with cysts and comedones

### Definitions

- Relatively common skin condition characterized by multiple open and closed comedones and cysts on sun-damaged skin of older adults

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- Exact mechanism unknown but thought to be due to chronic sun exposure
- Heavy smoking is often implicated
- Rare reports of therapeutic radiation as cause

## CLINICAL ISSUES

### Epidemiology

- Age
  - Often affects older patients (> 50 years)
- Sex
  - Generally seen in men
- Ethnicity
  - Typically affects Caucasian men
  - Rarely seen in darker skin types

### Site

- Symmetric distribution on temples and periocular areas
  - Other sites such as neck, postauricular areas, and forearms may also be affected

### Presentation

- Multiple open and closed comedones and cystic nodules on background of sun-damaged skin
  - In association with deep rhytides and waxy, yellowish hue of skin
- Generally seen in older (> 50 years of age) Caucasian men with history of significant sun exposure and cigarette smoking

### Treatment

- Combination of medical and surgical treatments offer best outcome
- Drugs
  - Topical retinoids (tretinoin, adapalene, tazarotene)
  - Oral isotretinoin
- Surgical approaches
  - Comedone extraction
  - Excision
  - Dermabrasion
  - Laser resurfacing
- Prevention of further actinic damage through meticulous sun protection is important
- Smoking cessation

### Prognosis

- FRS is benign but cosmetically displeasing

- Cutaneous malignancy may occur in association with FRS
  - However, there is no evidence of higher risk of malignant transformation in FRS than in actinically damaged skin elsewhere

## MICROSCOPIC

### Histologic Features

- Dilated pilosebaceous openings and cyst-like spaces filled with horny material
  - Often in association with of solar elastosis and epidermal atrophy
  - May be colonized with bacteria and Malassezia yeast
    - Bacteria include *Propionibacterium acnes*, *Corynebacterium* spp.

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Primary comedones of acne vulgaris
  - Indistinguishable histopathologically
    - However, inflammation is conspicuously absent in FRS
  - Surrounding skin of FRS shows marked solar elastosis
- Nodular solar elastosis
  - Lacks multiple comedones and cysts of FRS

### Clinical

- Chloracne
  - Often associated with occupational exposure to or accidental environmental poisoning with halogenated aromatic hydrocarbon compounds
  - Primarily closed comedones and cysts on malar cheeks and posterior ears
  - May also present as generalized acneiform eruption
- Milia
  - Small to minute monomorphic white cystic papules
- Colloid milium
  - Multiple, 1- to 3-mm translucent yellow papules in clusters
  - Neck, face, dorsal hands are favored sites

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# Collagenous and Elastotic Marginal Plaques of the Hands

## KEY FACTS

### TERMINOLOGY

- Synonyms
  - Keratoelastoidosis marginalis
  - Digital papular calcific elastosis

### ETIOLOGY/PATHOGENESIS

- Chronic sun damage

### CLINICAL ISSUES

- Translucent papules or small linear plaques
- Mostly arranged along radial and ulnar margins of hands
- Background sun damage prominent

### MICROSCOPIC

- Epidermal hyperplasia
- Hyperkeratosis
- Sparing of the papillary dermis
- Clumped and degenerated gray-blue elastic fibers in dermis
  - Elastic fibers may show calcification

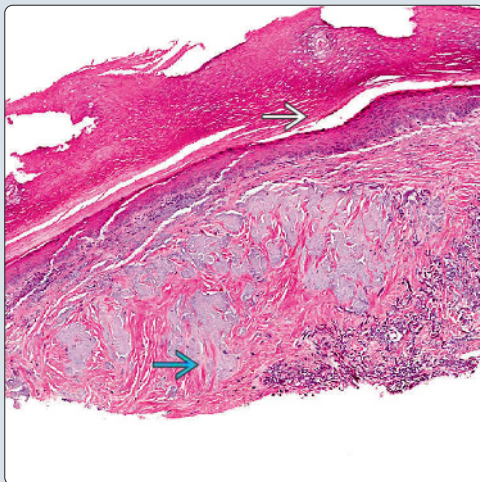
- Haphazardly arranged, fragmented collagen bundles

### TOP DIFFERENTIAL DIAGNOSES

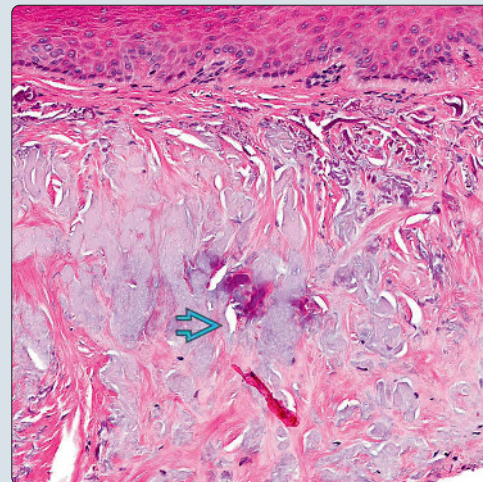
- Acrokeratoelastoidosis of Costa
  - Genodermatosis
  - Papules on hands and feet, no concomitant sun damage
  - Diminished and fragmented elastic fibers
  - No collagen fragmentation
- Nodular solar elastosis
  - Lacks calcification and collagen fragmentation
- Colloid milium
  - No calcifications
- Acquired elastotic hemangioma
  - Histology shows band-like proliferation of thin-walled capillaries arranged in parallel to epidermis
- Acrokeratosis verruciformis
  - Histology shows epidermal hyperplasia with papillomatosis and hyperkeratosis

Elastotic Material on Acral Skin

(Left) The acral location can be inferred by the presence of a thick cornified layer and a stratum lucidum. In the dermis, there are nodular aggregates of blue-gray clumped elastotic material. (Right) The papillary dermis is spared. In the reticular dermis there are nodular aggregates of blue-gray clumped elastic fibers. Focal calcification is characteristic.

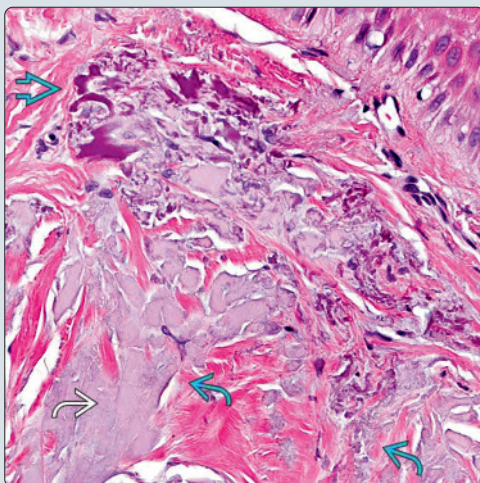


Calcification of Elastotic Material

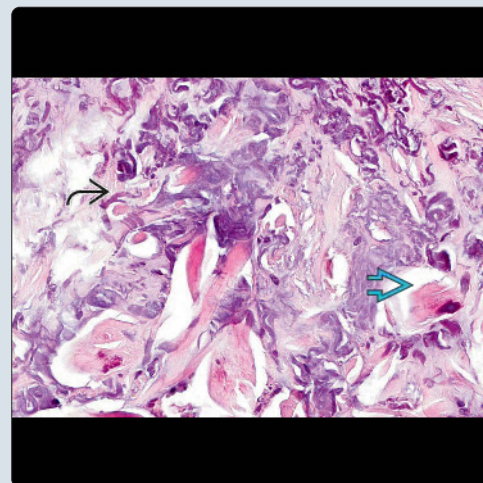


Collagenous and Elastotic Plaques

(Left) Plaques are formed by clumps of thick blue-gray elastic fibers. Integrated into the clumps are fragmented or haphazard collagen bundles. There are also basophilic foci representing calcification. (Right) High-power view shows coiling and clumping of thick elastic fibers. The admixed haphazardly arranged collagen bundles are also characteristic.



Thickened and Clumped Elastic Fibers





## TERMINOLOGY

### Abbreviations

- Collagenous and elastotic marginal plaques of hands (CEMPH)

### Synonyms

- Digital papular calcific elastosis
- Keratoelastoidosis marginalis

### Definitions

- Acquired hyperkeratotic plaques of marginal aspects of hands

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- Typically caused by chronic sun damage

## CLINICAL ISSUES

### Epidemiology

- Acquired disorder in elderly individuals with significant sun exposure

### Site

- Marginal aspects (radial and ulnar) of hands

### Presentation

- Begin as discrete translucent papules
- Over time, papules coalesce to form linear translucent plaques
- May see hyperkeratosis

### Treatment

- No treatment required

### Prognosis

- Chronic but benign condition

## MICROSCOPIC

### Histologic Features

- Acral skin: Thick cornified layer, stratum lucidum, lack of hair follicles
- Epidermis may be acanthotic, with hyperkeratosis
- Sparing of papillary dermis
- In reticular dermis there are nodular masses of gray-blue elastotic material, with focal calcification
- Fragmented and haphazardly arranged collagen bundles may be incorporated into elastotic masses
- Relative paucity of vessels
- Relative acellular matrix

## DIFFERENTIAL DIAGNOSIS

### Acrokeratoelastoidosis of Costa

- Genodermatosis
- Small indurated papules or plaques along margins of hands or feet
- No concomitant sun damage
- Hyperkeratosis with epidermal hyperplasia
- Elastic fibers are fragmented and diminished in number
- Lacks concomitant collagenous degeneration

### Nodular Solar Elastosis

- May occur in any location where chronic sun damage supervenes
- No calcification of elastic fibers
- No fragmentation or degeneration of collagen

### Colloid Milium

- Papillary dermal nodules of gray-blue elastotic material with fissures
- No calcifications

### Acquired Elastotic Hemangioma

- Appears on sun-damaged skin of dorsal forearms or lateral aspect of neck
- Mostly in women
- Solitary erythematous plaques
- Histology shows a band-like proliferation of thin-walled capillaries arranged in parallel to epidermis
  - Stroma shows solar elastosis
  - Endothelial cells may have plump cytology with protrusion into lumen

### Acrokeratosis Verruciformis

- Inherited disorder of cornification
- May be related to Darier disease
- Patients present with numerous flat topped papules on dorsal hands and feet
  - Resemble flat warts
- Histology shows epidermal hyperplasia with papillomatosis and hyperkeratosis
  - May have church spire morphology
  - Lacks dermal elastotic masses

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Characteristically seen on acral skin with chronic sun damage

### Pathologic Interpretation Pearls

- Acral skin shows thick cornified layer
- Papillary dermis spared
- Reticular dermis shows degenerated and clumped elastic fibers, with haphazardly arranged collagen bundles
- Stroma appears avascular and acellular

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## KEY FACTS

### TERMINOLOGY

- Synonyms include laptop thigh and toasted skin syndrome

### ETIOLOGY/PATHOGENESIS

- Chronic thermal radiation in range of 43-47° C, insufficient to result in burn

### CLINICAL ISSUES

- Reticulate hyperpigmentation with atrophy and telangiectasia due to chronic, repeated exposure to heat source
- Clinical findings may have geometric configuration, owing to shape of heat source

### MICROSCOPIC

- Squamous atypia and dysmaturation overlying telangiectasia and increased numbers of distorted elastic fibers and degenerated collagen

### ANCILLARY TESTS

- Verhoeff-van Gieson stain highlights distorted elastic fibers

### TOP DIFFERENTIAL DIAGNOSES

- Actinic keratosis
- Livedo reticularis
- Thermal burn
- Poikiloderma

### DIAGNOSTIC CHECKLIST

- Resembles actinic keratosis but with peculiar distorted elastic fibers instead of solar elastosis
  - Squamous atypia is also not limited to basal layer and overlying parakeratosis is often absent

Reticulate Erythema and Hyperpigmentation



*Erythema ab igne (EAI) presents as reticulate erythema and hyperpigmentation on the thigh simulating livedo reticularis. These cutaneous findings were preceded by chronic use of a portable heater.*

## TERMINOLOGY

### Abbreviations

- Erythema ab igne (EAI)

### Synonyms

- Fire stains
- Laptop thigh
- Toasted skin syndrome
- Hot water bottle rash
- Granny's tartan
- Erythema a calore
- Livedo reticularis e calore
- Ephelis ignealis
- Heat-induced circumscribed dermal melanosis

### Definitions

- Reticulate hypermelanosis induced by chronic thermal radiation
- EAI comes from Latin and means redness from fire

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- Prolonged, chronic thermal radiation in range of 43-47° C, insufficient to result in burn, is causative in EAI
- Historically, many reported cases were due to repeated exposure to open fires, heating pads, stoves, and electric blankets
- However, many reported cases now occur in patients using portable electronic devices, particularly laptop computers
- Skin findings may not present for weeks to months following chronic exposure to heating source

## CLINICAL ISSUES

### Site

- Although any anatomic location may be affected, most common sites of involvement are thighs, shins, and lower back

### Presentation

- Initially, erythematous macules or patches develop at site of heat exposure
- Later, reticulate hyperpigmentation, dusky erythema, scaling, atrophy, and telangiectasia develop
- Rarely, bullous lesions may occur
- Clinical findings may have geometric configuration, owing to shape of heat source
- Patients are generally asymptomatic
  - Although pruritus or burning sensation are occasionally reported

### Treatment

- Options, risks, complications
  - Successful treatment with low-fluency 1,064-nm Q-switched neodymium-doped yttrium aluminum garnet laser has been reported
- Drugs
  - Treatment with 5-fluorouracil cream has been reported to clear epidermal atypia in EAI

### Prognosis

- Treatment is not required but may be desired for reticulate hyperpigmentation, which is otherwise permanent
- Exposure to causative heat source should be discontinued given rare development of malignancy within EAI

## MICROSCOPIC

### Histologic Features

- Original histopathologic study of EAI described
  - Epidermal atrophy with diminished rete ridges
  - Atypical keratinocytes and dysmaturation
  - Telangiectasias in papillary dermis
  - Pigment incontinence
  - Degenerated collagen
  - Increase in dermal elastic tissue (elastosis)
- Additional features that may be seen include
  - Focal or confluent parakeratosis
  - Dyskeratosis
  - Vacuolar interface dermatitis
  - Melanocytic atypia
  - Hemosiderin deposition
- Bullous lesions demonstrate hydropic degeneration and subepidermal separation
- Malignancies have been reported to arise in setting of EAI, including
  - Squamous cell carcinoma
  - Primary cutaneous neuroendocrine (Merkel cell) carcinoma
  - Marginal zone lymphoma
  - Poorly differentiated carcinoma
- Reactive angioendotheliomatosis has also been described in association with EAI

## ANCILLARY TESTS

### Histochemistry

- Verhoeff-van Gieson stain highlights prominent dense band of narrow, curled, and branched elastic fibers in reticular dermis

## DIFFERENTIAL DIAGNOSIS

### Actinic Keratosis

- This is most difficult entity to distinguish on basis of histology alone
- Actinic keratoses typically have overlying parakeratosis
  - EAI usually shows basket weave stratum corneum but can show focal or confluent parakeratosis at times
- Epidermal atypia is also typically limited to basal layer
  - In EAI, squamous atypia can occur in all layers of epidermis and is often not limited to basal layer
- Clinical information is distinctive for EAI
  - EAI often occurs on nonsun-exposed sites

### Livedo Reticularis

- Clinical appearance and site of involvement may be very similar
- Livedo reticularis demonstrates
  - Red blood cell aggregates in superficial vessels
  - Vessel wall thickening and thrombus in deep dermis



- Occasionally vasculitis with obliteration of deep dermal or subcutaneous arteries
- Epidermal atypia and elastosis are absent

## Thermal Burn

- Necrosis (mummification) and cytolysis are characteristic of thermal burns and lacking in EAI
- 1st-degree burns only involve epidermis with sparing of basal layer
  - 2nd-degree burns involve superficial dermis
  - 3rd-degree burns involve complete dermis

## Poikiloderma

- Vacuolar change, telangiectasia, and elastosis are shared features
- Keratinocyte atypia, dyskeratosis, and dysmaturation are not seen in poikiloderma

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Epidermal atrophy
- Keratinocyte atypia
- Dyskeratosis
- Telangiectasia
- Increased dermal elastic tissue (elastosis)

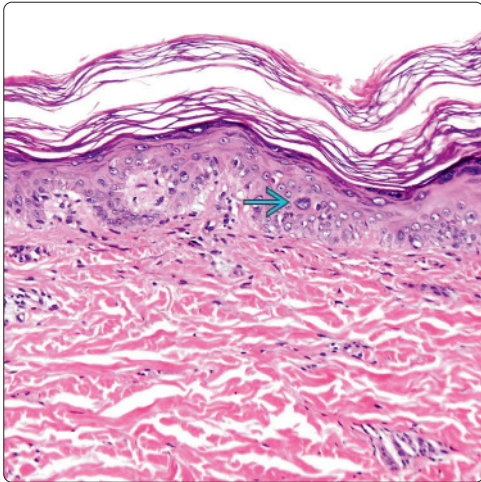
### Pathologic Interpretation Pearls

- Resembles actinic keratosis but with peculiar distorted elastic fibers instead of solar elastosis

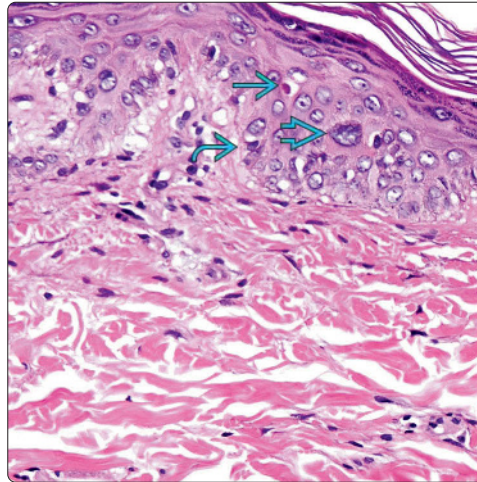
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**Squamous Atypia and Dysmaturation**



**Squamous Atypia and Necrotic Keratinocytes**



(Left) Histologic findings may be subtle and are analogous to those found in actinic keratosis: Squamous atypia with dysmaturation. Note the absence of parakeratosis overlying. (Right) Histology demonstrates squamous atypia with dysmaturation, rare necrotic keratinocytes, and subtle vacuolar change.

**Geometric Outline**

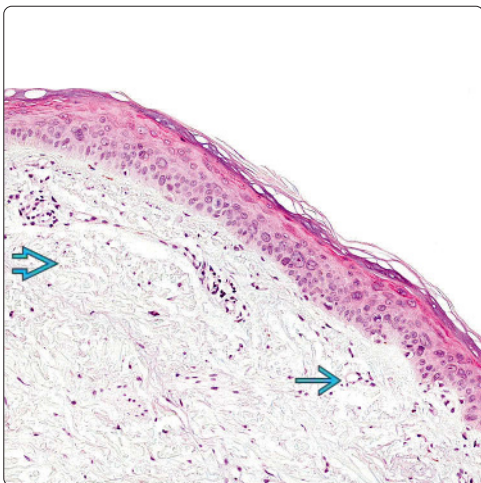


**Chronic Heating Pad Use**

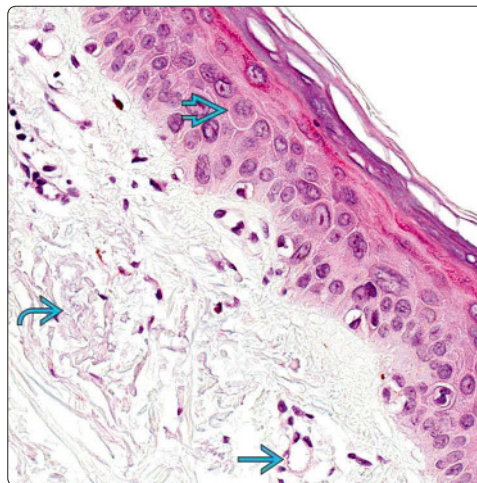


(Left) EAI clinically presents as reticulate erythema and hyperpigmentation. Note the geometric outline, corresponding to exposure to an external heat source. (Right) This case of EAI resulted from chronic use of a heating pad applied to the back. (Courtesy S. Hsu, MD.)

**Epidermal Atypia Overlying Elastosis and Telangiectasia**



**Epidermal Atypia, Telangiectasia, and Elastosis**



(Left) Epidermal atypia overlying elastosis (disordered elastic fibers) and telangiectasia is shown. Note the epidermal atrophy with diminished rete ridges. (Right) High-power view shows epidermal atypia, telangiectasia, and elastosis. Also note the basket-weave stratum corneum overlying. Parakeratosis will typically be present in an actinic keratosis.



## Anetoderma

## KEY FACTS

## CLINICAL ISSUES

- Age
  - Presents usually between 20-40 years of age
- Sex
  - Female preponderance
- Numerous up to 3-cm foci of flaccid skin
- May have bulging appearance
- Primarily found on trunk and upper extremities
- Overlying dermis may be wrinkled or atrophic
- Primary anetoderma
  - Significant association with antiphospholipid antibodies
    - Lupus anticoagulant
    - Anticardiolipin antibody
  - Associated with myriad of autoimmune diseases
- Secondary anetoderma
  - Wide range of associations including infection, HIV infection, lymphoma, hepatitis B vaccination, and many others

## MICROSCOPIC

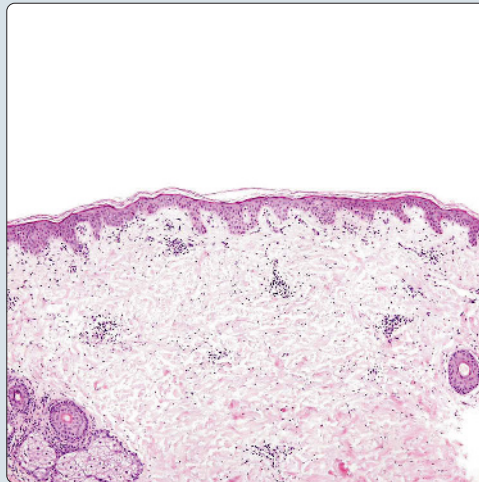
- Markedly decreased or completely absent elastic fibers in papillary and reticular dermis
  - Elastic fibers may be fragmented
- Early lesions may show inflammatory infiltrate
  - May consist of lymphocytes, histiocytes ( $\pm$  granulomata), &/or plasma cells
    - Elastophagocytosis may uncommonly be present
- Later lesions may be easily mistaken for normal skin

## TOP DIFFERENTIAL DIAGNOSES

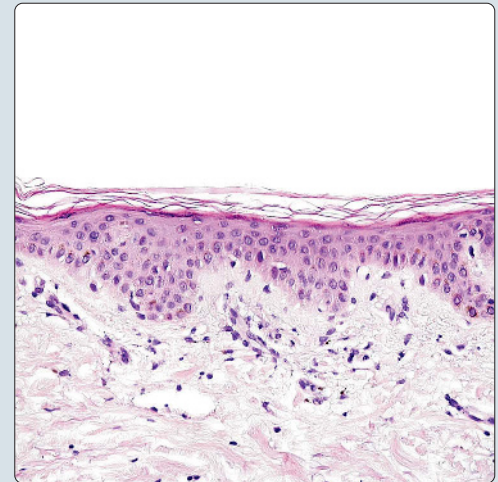
- Mycosis fungoides
- Tinea versicolor
- Cutis laxa
- Pseudoxanthoma elasticum-like papillary dermal elastolysis
- Perifollicular elastolysis
- Middermal elastolysis

## Sparse Inflammatory Infiltrate


**(Left)** Specimens from patients with anetoderma typically have a sparse lymphocytic inflammatory cell infiltrate. Very few other changes are readily identified. **(Right)** The overlying epidermis is unremarkable. The cornified layer consists of basket-weave keratin. Acanthosis is not present. No hyperpigmentation is identified.

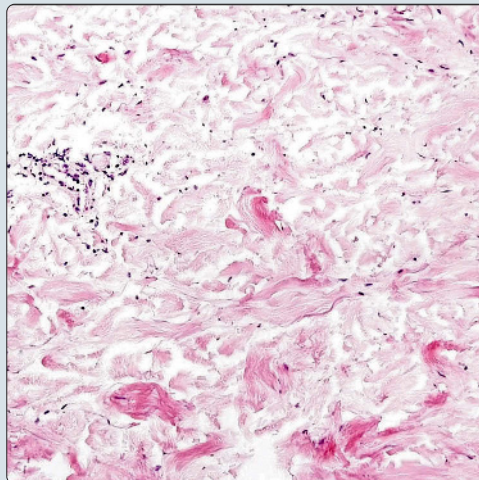


## Normal Epidermis



## Collagen Appears Normal

**(Left)** Routine staining shows normal collagen bundles throughout the dermis. Elastic fibers may be present, but they can be difficult to identify with hematoxylin and eosin. **(Right)** The diagnostic changes of anetoderma are best appreciated with an elastic stain. The elastic fibers, which appear black using this technique , are markedly reduced or absent throughout the dermis.



## Decreased or Absent Elastic Fibers





**TERMINOLOGY****Definitions**

- Numerous small foci of slack skin on trunk and proximal extremities
  - Anetos = slack

**CLINICAL ISSUES****Epidemiology**

- Age
  - Presents usually between 20-40 years of age
- Sex
  - Female preponderance

**Presentation**

- Numerous up to 3-cm foci of flaccid skin
  - May have bulging appearance
- Primarily found on trunk and upper extremities
  - Other sites may be involved
- Overlying dermis may be wrinkled or atrophic
- Jadassohn-Pellizzari subtype
  - Usually erythematous and preceded by inflammatory lesion
- Schweninger-Buzzi subtype
  - Typically not preceded by inflammatory lesion
- Primary anetoderma
  - Significant association with antiphospholipid antibodies
    - Lupus anticoagulant
    - Anticardiolipin antibody
  - Associated with myriad of autoimmune diseases
- Secondary anetoderma
  - Wide range of associations including infection, HIV infection, lymphoma, hepatitis B vaccination, and many others

**Treatment**

- Lasers
  - 595-nm pulsed-dye laser and 1550-nm non-ablative fractionated laser has been reported to increase elastic fibers and improve disease appearance

**Pathogenesis**

- Not completely understood
- Imbalance in matrix metalloproteinases and their inhibitors has been demonstrated
- Association with autoimmunity suggests immunological etiology
  - Antibodies to elastic fibers have not been identified

**MICROSCOPIC****Histologic Features**

- Markedly decreased or completely absent elastic fibers in papillary and reticular dermis
  - Elastic fibers may be fragmented
- Early lesions may show inflammatory infiltrate
  - May consist of lymphocytes, histiocytes ( $\pm$  granulomata), &/or plasma cells
    - Elastophagocytosis may uncommonly be present
- Later lesions may be easily mistaken for normal skin

**ANCILLARY TESTS****Histochemistry**

- Elastic van Gieson (Verhoeff-van Gieson)
  - Positive in any residual elastic fibers

**Immunofluorescence**

- IgG and C3 granular positivity along basement membrane

**DIFFERENTIAL DIAGNOSIS****Histopathological**

- Cutis laxa
  - Loose, hanging skin
  - Marked decrease in elastic fibers within papillary and reticular dermis
  - May have inflammatory infiltrate
  - Clinical appearance is critical for differentiation
- Pseudoxanthoma elasticum-like papillary dermal elastolysis
  - Yellow or flesh-colored small plaques on neck in older women
  - Complete loss of elastic fibers in papillary dermis only
  - Reticular dermal elastic fibers are not affected
- Perifollicular elastolysis
  - 2- to 4-mm lesions with central hair follicle
  - May have slight bulging as seen in anetoderma
  - Likely represent healed and scarred areas of acne
  - Loss of elastic fibers is centered around hair follicles
- Middermal elastolysis
  - Sun-exposed areas of trunk, neck, and upper extremities
  - Can present in multiple different ways
    - Type 1: Wrinkling following Blaschko lines
    - Type 2: Perifollicular papules, which may even have peau d'orange appearance
    - Type 3: Reticular pattern of wrinkling with associated erythema
  - Loss of elastic fibers is centered in middermis

**Clinical**

- Mycosis fungoides
  - Some lesions of mycosis fungoides may have small plaques with overlying fine scale
    - Usually accompanied by larger more geometric lesions
  - Malignant T-cell infiltration with epidermotropism
- Tinea versicolor
  - May appear atrophic in some patients
  - Fungal organisms are present in stratum corneum

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## KEY FACTS

### TERMINOLOGY

- Inherited or acquired disease resulting in abnormal elastic fibers

### ETIOLOGY/PATHOGENESIS

- Inherited cutis laxa (CL) results from genetic mutations affecting elastin metabolism, while acquired CL results from medications and underlying conditions

### CLINICAL ISSUES

- All forms of CL demonstrate loose, redundant, hypoelastic skin
- *FBLN5* and *FBLN4* mutations

### MICROSCOPIC

- Quantitative or qualitative abnormalities in elastic fiber content

### ANCILLARY TESTS

- Special stains for elastin, such as Verhoeff-van Gieson

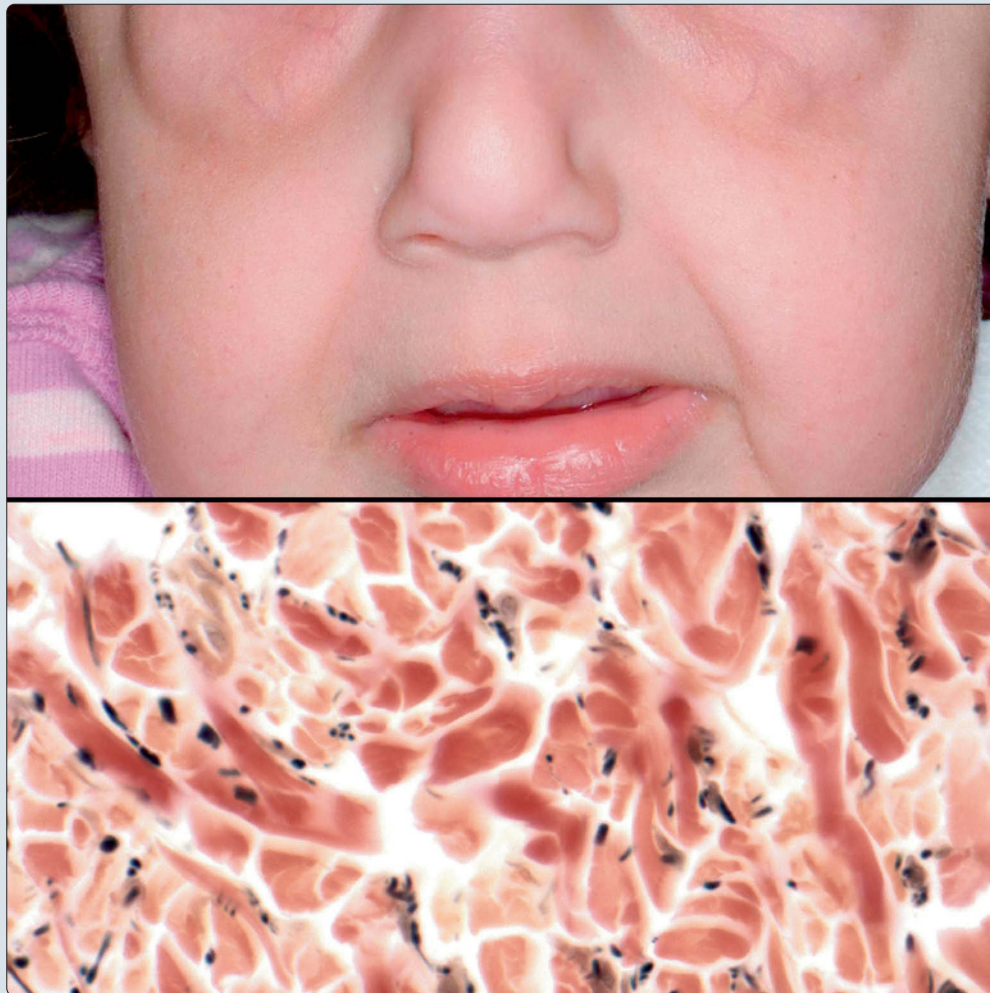
### TOP DIFFERENTIAL DIAGNOSES

- Anetoderma
- Middermal elastolysis
- Pseudoxanthoma elasticum
- Ehlers-Danlos syndrome

### DIAGNOSTIC CHECKLIST

- Special stain for elastin should be performed in all suspected cases
- Clinicopathologic correlation is often required to distinguish from other elastolytic disorders

## Sagging Skin and Shortened Elastic Fibers



Upper photo shows a 2-year-old girl with fibulin-4 deficiency who demonstrates sagging infraorbital and cheek skin of cutis laxa. Bottom image shows elastic fibers that are shortened, vary in diameter, and have indistinct, hazy borders on Verhoeff-van Gieson stain. (Bottom image from Hurwitz Clinical Pediatric Dermatology, 5e.; top image from Weedon's Skin Pathology, 4e.)

## TERMINOLOGY

### Abbreviations

- Cutis laxa (CL)

### Synonyms

- Generalized elastolysis, Debre syndrome, De Barsy syndrome, Marshall syndrome

### Definitions

- Exceedingly rare systemic disease affecting elastic tissue with both familial and acquired variants

## ETIOLOGY/PATHOGENESIS

### Developmental Anomaly

- Elastic fibers normally provide resilience to skin and contain amorphous core as well as microfibrils, which act as scaffolding for extracellular matrix proteins
  - Mutations in genes encoding elastin, fibulin, and copper transporter ATP7A are all associated with inherited forms of CL
- In contrast, acquired forms of CL are associated with medications, such as penicillin, lymphoproliferative disorders, spirochete infections, and autoimmune connective tissue disease

## CLINICAL ISSUES

### Presentation

- Autosomal recessive variants
  - Infants may have loose, redundant skin folds (bloodhound appearance) in dependent regions of body
  - Skin is completely devoid of elastic recoil
  - Type 1
    - Prototypic CL
    - Cutaneous, pulmonary, and vascular lesions with diverticula
  - Type 2 (Debre type)
    - CL features with bone dystrophy, congenital hip dislocation, and mental retardation
  - Type 3 (De Barsy syndrome)
    - CL with progeria, corneal clouding, athetosis, and mental retardation with brain dysgenesis (cobblestone-like)
- Autosomal dominant
  - Usually mild
- X-linked recessive (occipital horn syndrome)
  - CL with hyperextensible joints, decreased wound healing, bladder diverticula, and mild mental retardation
- Acquired variants
  - Features are variable, ranging from localized cutaneous condition, to serious, potentially life-threatening systemic condition
  - Postinflammatory elastolysis and CL (Marshall syndrome)
  - Adult generalized acquired CL
  - Localized CL

## MICROSCOPIC

### Histologic Features

- Under routine microscopy, biopsies of CL appear normal

- Elastin stains, such as orcein, Verhoeff-van Gieson (VVG), or Weigert, should be used for evaluation in suspected cases
- All inherited and acquired variants of CL show some degree of elastic fiber abnormality, but no histologic findings allow clear distinction between variants of CL or anetoderma
  - Thus, elastin stains are sensitive but not specific for CL
- Paucity of elastin fibers (elastin in papillary dermis) is observed in autosomal recessive and autosomal dominant forms of CL, while underdeveloped or globular deposits of elastin may be seen in reticular dermis
- Absence of elastic fibers, analogous to that seen in anetoderma, may also be seen
- Occasionally, very mild abnormalities in elastin may not be detected by special stains, such as VVG
- In Marshall syndrome, nodular diffuse infiltrates of neutrophils precede elastolysis

## ANCILLARY TESTS

### Histochemistry

- Special stain for elastin, such as orcein, VVG, or Weigert, should be used for evaluation in all suspected cases of CL

## DIFFERENTIAL DIAGNOSIS

### Ehlers-Danlos Syndrome

- Ehlers-Danlos syndrome (EDS), unlike CL, is characterized by hyperelasticity, meaning that skin snaps back into place quickly upon stretching
- Histopathology demonstrates unremarkable-appearing skin, although large and irregular collagen fibers are described
- Unlike CL, special stains demonstrate normal quantity and quality of elastic fibers in EDS

### Pseudoxanthoma Elasticum

- Hypoelasticity is feature common to both pseudoxanthoma elasticum and CL
- Clumped, fragmented, and calcified elastic fibers are present on histology and can be identified by special stains for elastin and calcium

### Anetoderma

- Anetoderma demonstrates total loss of elastic fibers, which may also be found in CL
  - Thus, clinical distinction is required
- Anetoderma is described as discrete, flaccid patches or plaques of slack skin, with overlying wrinkling, most often on trunk or extremities

### Middermal Elastolysis

- In middermal elastolysis, focal loss of elastin is found, with preservation of reticular and papillary elastic fibers

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## KEY FACTS

### TERMINOLOGY

- Rare autosomal dominant genodermatosis (may also occur sporadically) characterized by multiple small yellowish papules symmetrically distributed on sides of both hands and feet

### ETIOLOGY/PATHOGENESIS

- History of chronic sun exposure and chronic trauma is thought to play role

### CLINICAL ISSUES

- Multiple yellowish, 2- to 4-mm papules (often umbilicated) symmetrically disposed at lateral margins of hands and feet
- Sporadic cases often in older individuals
- Autosomal dominant cases often in young adults (20-30 years old)
- Symmetry is characteristic
- Treatment is generally not required but may be done for cosmetic reasons

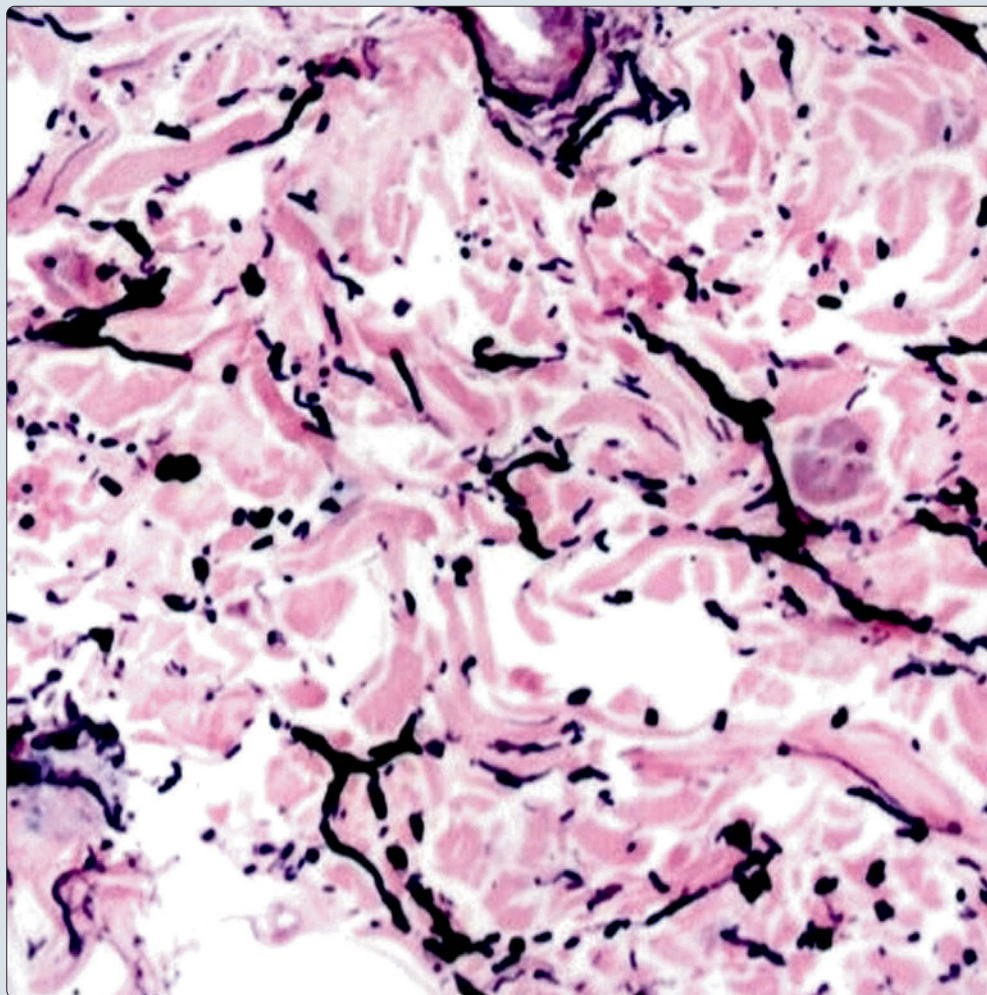
### MICROSCOPIC

- Hyperkeratosis
- Hyalinized and homogenous collagen
- Elastorrhexis and decreased elastic fibers
- Elastic fibers are curled and fragmented (elastorrhexis)

### TOP DIFFERENTIAL DIAGNOSES

- Acrokeratoelastoidosis-like lesions in scleroderma
  - Clinical history of systemic scleroderma or localized nodular scleroderma is necessary to differentiate
- Amyloidosis
  - Elastorrhexis is absent
- Degenerative collagenous plaques of hands
  - Dense deposition of collagen tissue on biopsy (vs. decreased and fragmented elastic fibers)
- Keratoelastoidosis marginalis
- Solar elastosis
- Actinic granuloma (O'Brien)

Elastorrhexis (Curled and Fragmented Elastic Fibers)



An Orcein stain demonstrates fragmented elastic fibers (elastorrhexis) in the reticular dermis. (Courtesy M. Costa, MD.)

## TERMINOLOGY

### Synonyms

- Acrokeratoelastoidosis of Costa
- Acrokeratoelastoidosis of Oswaldo Costa
- Inverse papular acrokeratosis
- Lichenoid acrokeratoelastoidosis

### Definitions

- Rare autosomal dominant genodermatosis (may also occur sporadically) characterized by multiple small yellowish papules symmetrically distributed on sides of both hands and feet

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- History of chronic sun exposure and chronic trauma is thought to play role
  - Commonly elucidated from patients

### Unknown Etiology

- Studies suggest disease may be due to abnormality in secretion of elastic fibers from fibroblasts rather than abnormality in fiber degradation
- Some hypothesize that disease could be due to generalized defect in elastic tissue somehow limited in location

### Inheritance

- Autosomal dominant, has been linked to chromosome 2

## CLINICAL ISSUES

### Epidemiology

- Age
  - Sporadic cases often in older individuals
  - Autosomal dominant cases often in young adults (20-30 years old)
- Ethnicity
  - More common in black women

### Presentation

- Multiple yellowish, 2- to 4-mm papules (often umbilicated) symmetrically disposed at lateral margins of hands and feet
  - Symmetry is characteristic
- Skin thickening can occur over proximal interphalangeal as well as metacarpophalangeal and metatarsophalangeal joints
- Rapid progression has been reported in pregnancy

### Treatment

- Options, risks, complications
  - Treatment is generally not required but may be done for cosmetic reasons
  - Numerous drugs have been tried but little improvement is usually achieved
- Surgical approaches
  - Cryosurgery and Er:YAG can be used but usually with little improvement
- Drugs
  - Acitretin
    - Appears to be most effective; however, lesions recur upon discontinuation of treatment

### Prognosis

- Excellent
  - Condition is not life-threatening and mainly cosmetic nuisance

## MICROSCOPIC

### Histologic Features

- Hyperkeratosis
  - Can cause depression of overlying epidermis creating concavity
- Hypergranulosis
- Mild acanthosis
- Hyalinized and homogenous collagen
- Elastorrhexis and decreased elastic fibers
  - Elastic fibers are curled and fragmented (elastorrhexis)

## ANCILLARY TESTS

### Histochemistry

- Verhoeff-Van Gieson, Orcein, or Weigert stain
  - Can help highlight changes in elastic fibers

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Acrokeratoelastoidosis-like lesions in scleroderma
  - Histopathology is similar
  - Clinical history of systemic scleroderma or localized nodular scleroderma is necessary
- Amyloidosis
  - Stains positively with amyloid immunostains or Congo red
  - Elastorrhexis is absent
- Degenerative collagenous plaques of hands
  - Dense deposition of collagen tissue on biopsy (vs. decreased and fragmented elastic fibers)
- Keratoelastoidosis marginalis
  - Clinically only affects hands
  - Shows solar elastosis with thickened, fragmented, often calcified elastic fibers between degenerated collagen bundles
- Solar elastosis
  - Elastic fibers lack fragmentation or thickening
- Actinic granuloma (O'Brien)
  - Elastorrhexis along with palisaded granulomatous dermatitis
  - Many authors consider this variant of granuloma annulare that occurs on sun-exposed skin

## SELECTED REFERENCES

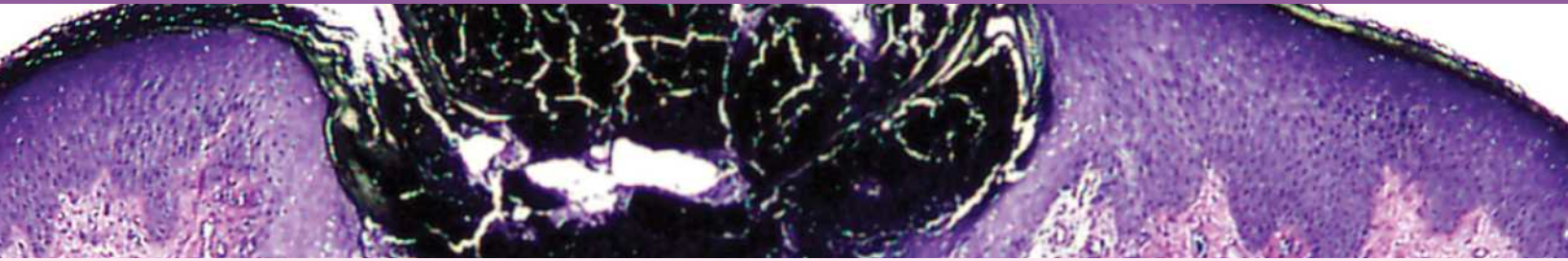
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## SECTION 7

# Degenerative and Perforating Diseases



Chondrodermatitis Nodularis Helicis

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Perforating Dermatoses

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Elephantiasis Nostras Verrucosa

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# Chondrodermatitis Nodularis Helicis

## KEY FACTS

### TERMINOLOGY

- Small, nodular, usually solitary, and tender chronic inflammatory lesion of outer helix of ear that is usually result of trauma

### CLINICAL ISSUES

- Lesions are often 2-6 mm in diameter and appear as well-developed, ovoid, reddish, and tender masses that have usually been present for several years

### MICROSCOPIC

- Usually central, crateriform ulcer often with scale crust is present with acanthosis, hyperkeratosis, and parakeratosis of adjacent epithelium
- Underlying crater is dermal fibrinoid degeneration of collagen and necrosis
- Base of lesion is composed of granulation tissue and occasionally chronic inflammatory infiltrate
- Telangiectatic vessels and solar elastosis in adjacent dermis

- Cartilage is typically uninvolved

### TOP DIFFERENTIAL DIAGNOSES

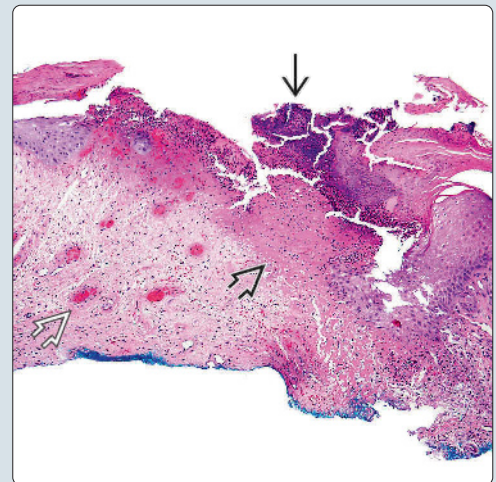
- Relapsing polychondritis
  - Patients typically have polyarthritis and nasal involvement
  - Mixed inflammatory infiltrate in dermis surrounding cartilage with pyknotic and vacuolated chondrocytes lacking basophilia
  - Histologically, chondrocytes are destroyed and replaced by fibrous tissue
- Ulcer/excoriation
  - Superficial biopsies can at times make differentiation impossible
  - Excoriation should be more superficial and lacks fibrin and telangiectatic vessels
- Weathering nodules of ear
- Basal cell carcinoma or squamous cell carcinoma (clinically)

**Painful Yellow Crust With Surrounding Erythema**

(Left) *Chondrodermatitis nodularis helicis* (CNH) on the superior helix of the ear shows a central dry, adherent, yellowish crust and surrounding erythema. It was exquisitely painful when the patient turned in bed and laid on it. (Right) Classic biopsies of CNH demonstrate a central crusted ulcer, underlying fibrin deposition, and granulation tissue at the base. (Courtesy K. Duffy, MD.)



**Crusted Ulcer, Fibrin Deposition, and Granulation Tissue**

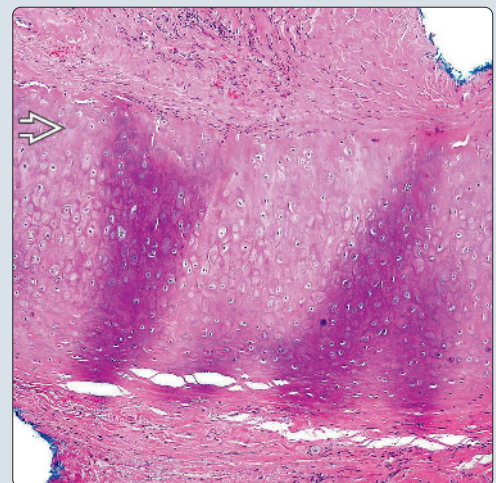


**Central Ulcer With Adjacent Telangiectasia**

(Left) More superficial biopsies can still be easily recognized as CNH with a central ulcer, adjacent dermal telangiectatic vessels, and adjacent parakeratosis. (Courtesy A. Bowen, MD.) (Right) Deeper biopsies may demonstrate cartilage that is typically uninvolved (vs. relapsing polychondritis). (Courtesy A. Bowen, MD.)



**Uninvolved Cartilage**



## TERMINOLOGY

### Abbreviations

- Chondrodermatitis nodularis helicis (CNH)

### Synonyms

- Chondrodermatitis nodularis chronica helicis

### Definitions

- Small, nodular, usually solitary, and tender chronic inflammatory lesion of outer helix of ear that is usually result of trauma

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- History of chronic solar exposure, physical trauma, or frostbite are common histories from patients
  - True pathophysiology is likely multifactorial
    - CNH may represent attempt at transepidermal elimination of degenerated collagen by dermis
  - Cartilage degeneration is believed to be secondary to these environmental exposures
  - Some cases are secondary to poor vascular supply

## CLINICAL ISSUES

### Epidemiology

- Age
  - Often older men > 40 years of age (average: 60 years)
- Sex
  - M > F
    - Uncommonly affects female patients (estimate 10-35% of cases), but, when it does, there is predilection for antihelix

### Presentation

- Lesions are often 2-6 mm in diameter and appear as well-developed, ovoid, reddish, and tender masses that have usually been present for several years
- Although usually solitary, multiple lesions may line outer rim of helix
- Lesions are firmly attached to underlying cartilage
- Adherent scale or ulcer is also often present overlying lesions
- Clinically, these lesions may mimic basal cell carcinoma or squamous cell carcinoma
  - Biopsy easily establishes diagnosis, and there is no risk of malignant transformation

### Treatment

- Options, risks, complications
  - Single or multiple intralesional steroid injections will cure ~ 1/2 of cases
    - Remainder of cases typically require surgery
  - Pressure-relieving devices may be of some help
- Surgical approaches
  - Removing underlying cartilage alone may produce best cosmetic results and low recurrence rate
  - Excision of overlying skin and portion of underlying cartilage is another option
  - Recurrence rate is high (~ 20%) especially if underlying, damaged cartilage is not removed

## Prognosis

- Generally excellent with recurrence after surgery being main problem
  - Main reason for medical or surgical treatment is unrelenting pain

## MICROSCOPIC

### Histologic Features

- Usually central, crateriform ulcer often with scale crust is present with acanthosis, hyperkeratosis, and parakeratosis of adjacent epithelium
- Underlying crater is dermal fibrinoid degeneration of collagen and necrosis
  - Edema of underlying dermis may be prominent
- Base of lesion is composed of granulation tissue and occasionally chronic inflammatory infiltrate
- Cartilage is typically uninvolved
  - Minimal cartilaginous degeneration may occur
  - Mild perichondrial chronic inflammatory infiltrate may be seen
  - Healed lesions may show fibrosis of dermis and perichondrium
- Telangiectatic vessels and solar elastosis may be present in adjacent dermis
- Often biopsies are more superficial or out of plain of section
  - CNH may still be easily recognized by dermal fibrin deposition as well as adjacent parakeratosis, acanthosis, and dermal telangiectatic vessels

## DIFFERENTIAL DIAGNOSIS

### Histopathologic Differential Diagnosis

- **Relapsing polychondritis**
  - Patients typically have polyarthritis and nasal involvement
  - Mixed inflammatory infiltrate in dermis surrounding cartilage with pyknotic and vacuolated chondrocytes lacking basophilia
  - Histologically, chondrocytes are destroyed and replaced by fibrous tissue
- **Ulcer/excoriation**
  - Superficial biopsies can, at times, make differentiation impossible
  - Excoriation should be more superficial and lacks fibrin and telangiectatic vessels
  - Clinically, should have other excoriations or changes of lichen simplex chronicus in other areas

### Clinical Differential Diagnosis

- **Basal cell carcinoma** and **squamous cell carcinoma**
  - Histology easily distinguishes from CNH
- **Weathering nodules of ear**
  - Histology shows spur of fibrous tissue with focus of cartilaginous metaplasia

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# Perforating Dermatoses

## KEY FACTS

### TERMINOLOGY

- Kyrle disease
  - Large papules with central keratin plugs that typically appear in widespread distribution and bilaterally
- Perforating folliculitis
  - Follicular-based eruptions of nodules and papules with histologic demonstration of transepidermal elimination of altered dermal connective tissue
- Reactive perforating collagenosis
  - Inherited or acquired skin disorder characterized by flesh-colored papules that demonstrate transepidermal elimination of collagen
- Elastosis perforans serpiginosa (EPS)
  - Rare disease that presents as annular or serpiginous keratotic papules on face and neck and involves transepidermal elimination of altered elastic fibers
- Acquired perforating dermatosis
  - Perforating dermatosis arising in adult patients

### MICROSCOPIC

- Significant overlap of all entities
  - Common finding is transepidermal elimination of amorphous debris, which differs depending on disease
  - Often can see combination of elastic, keratin, and collagen fibers in lesions regardless of etiology

### TOP DIFFERENTIAL DIAGNOSES

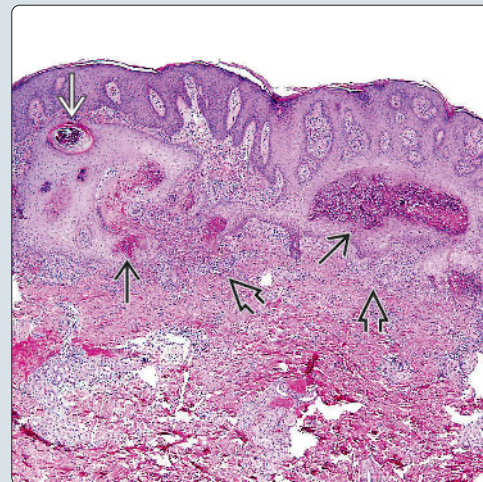
- Periumbilical perforating pseudoxanthoma elasticum
  - Fragmented, clumped, calcified elastic fibers in midlower dermis extruded by transepidermal elimination (EPS noncalcified, more superficial)
- Perforating granuloma annulare
  - Histology still shows characteristic palisading granulomas composed of necrobiotic collagen, mucin, and fibrin surrounded by lymphocytes and histiocytes

**Nodules With Keratotic Center**

**(Left)** Perforating folliculitis in this renal transplant patient demonstrates nodules having a central keratotic center and showing koebnerization over the anterior thighs. **(Right)** Biopsy of a patient with perforating folliculitis shows degenerated collagen fibers perforating through and extending into the hair follicle epithelium with surrounding inflammation.

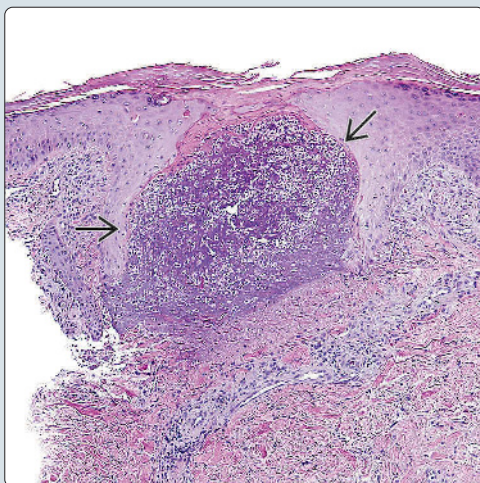


**Degenerated Collagen Fibers**

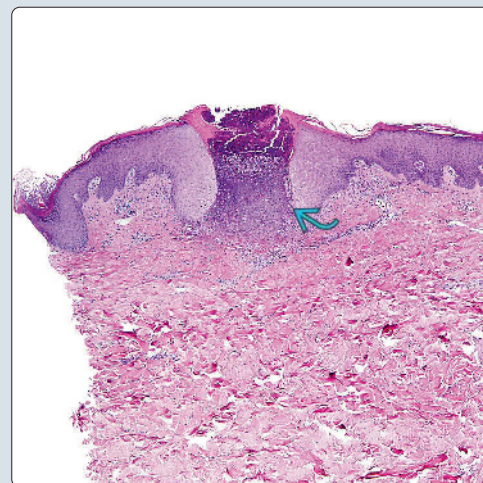


**Transepidermal Elimination of Amorphous Material**

**(Left)** This perforating disorder shows a cup-shaped invagination of amorphous material being transepidermally eliminated. An elastin, collagen stain, and clinical history would help determine etiology. **(Right)** This low-power view of a punch biopsy of a perforating disorder demonstrates transepidermal elimination of collagen through a central plug.



**Low-Power View of Transepidermal Elimination**



## TERMINOLOGY

### Definitions

- Group of dermatoses related by common finding of transepidermal elimination of amorphous debris on biopsy, which differs according to specific disease
- **Kyrle disease** (hyperkeratosis follicularis et para-follicularis in cutem penetrans)
  - Large papules with central keratin plugs that typically appear widespread and bilaterally
- **Perforating folliculitis**
  - Follicular-based eruptions of nodules and papules with histologic demonstration of transepidermal elimination of altered dermal connective tissue
- **Reactive perforating collagenosis**
  - Inherited or acquired skin disorder characterized by flesh-colored papules that demonstrate transepidermal elimination of collagen
- **Elastosis perforans serpiginosa (EPS)**
  - Rare disease that presents as annular or serpiginous keratotic papules on face and neck and involves transepidermal elimination of altered elastic fibers
- **Acquired perforating dermatosis**
  - Perforating dermatosis arising in adult patients
  - Clinical and histologic features may resemble any of 4 primary perforating dermatoses

## ETIOLOGY/PATHOGENESIS

### Kyrle Disease

- Unknown, but postulated to be related to abnormal and rapid keratinization
- Associated with renal failure, diabetes mellitus, congestive heart failure, and hepatic insufficiency
- May have significant overlap with perforating folliculitis (some debate its existence)

### Perforating Folliculitis

- Unknown, but trauma is thought to play role
- Can be associated with renal failure, HIV infection, and, rarely, primary sclerosing cholangitis

### Reactive Perforating Collagenosis

- Unknown, but autosomal recessive and autosomal dominant inheritance has been described
  - No underlying disorder in inherited forms
- Acquired or adult-onset disease can be associated with
  - Chronic renal failure, diabetes, IgA nephropathy, herpes zoster, scabies, AIDS, lymphoma, Treacher Collins syndrome, and others

### Elastosis Perforans Serpiginosa

- Pathogenesis not fully understood
- Occurs in 3 forms
  - Idiopathic EPS has unknown cause, although it is believed to be genetic
  - Drug-induced EPS occurs in ~ 1% of patients treated with penicillamine
  - Reactive EPS is form associated with variety of systemic, inherited, or connective tissue disorders

### Acquired Perforating Dermatitis

- Multiple theories, including

- Microtrauma from itching and pruritus, deposition of substances dialysis cannot remove, microangiopathy, epidermal changes from metabolic derangements

## CLINICAL ISSUES

### Epidemiology

- Age
  - Kyrle disease: 3rd-7th decades
  - Perforating folliculitis: Typically 2nd-4th decades
  - Reactive perforating collagenosis
    - Inherited form: Infancy or early childhood
    - Acquired form: Adults
  - EPS: Varies from early childhood to late adulthood (typically 2nd decade)
  - Acquired perforating dermatosis: Mean age = 48 years
- Sex
  - Kyrle disease: M = F
  - Reactive perforating collagenosis: M = F
  - Perforating folliculitis: M < F (1:2)

### Presentation

- Kyrle disease
  - Widespread often bilateral eruption of asymptomatic hyperkeratotic, verrucous nodules and papules
    - Nodules are follicular based and contain central keratin plug
  - Typically occur on trunk, extremities, face, scalp, or neck
  - Palms, soles, and mucous membranes spared
- Perforating folliculitis
  - Erythematous, follicular-based infiltrating papules and nodules most commonly occurring on extensor surface of extremities and on buttocks
  - Papules typically contain central keratotic core
  - Koebner phenomenon typically absent (vs. other perforating dermatoses)
- Reactive perforating collagenosis
  - 2 distinct clinical variants occurring in childhood and adulthood (acquired)
  - Childhood form presents with recurrent flesh-colored papules that enlarge from 1-2 mm to 5-10 mm over course of several weeks, become umbilicated, and then regress
    - After 6-8 weeks, hypopigmentation or scar remains
    - New lesions develop as older lesions heal
    - This cycle can continue into adulthood
  - Adult form
- EPS
  - Keratotic papules form ring with slightly atrophic center, especially on neck
- Acquired perforating dermatosis
  - Few to many lesions most commonly occurring on extensor surfaces of lower extremities
  - Lesions clinically resemble any 1 of primary perforating dermatoses
  - Usually arises with renal disease, but other conditions reported

### Treatment

- No single treatment is uniformly successful

# Perforating Dermatoses

- Surgical approaches often do more harm than good, as they may cause scarring; however, cryotherapy has been used with some success
- For itching and inflammation, topical, intralesional, and steroids under occlusion have been successful
- Multiple case reports of various successful drugs
  - Topical or oral retinoids, vitamin A, keratolytics, allopurinol, and allopurinol with PUVA, others

## Prognosis

- Disease course is benign with some cases resolving after years
  - Unfortunately, in those that do not resolve, therapy is often unsatisfactory with new disease appearing
  - Management of pruritus and even pain, especially in perforating folliculitis, is difficult to control
- Rare systemic disease does exist that can lead to death if abnormal elastic tissue involves and ruptures blood vessels

## MICROSCOPIC

### Histologic Features

- Significant overlap of all 5
- Kyrle disease
  - Epidermal invagination filled with keratin, degenerated cellular and inflammatory debris
- Perforating folliculitis
  - Dilated hair follicle with keratinous and basophilic cellular debris surrounded by mixed inflammatory infiltrate with karyorrhexis
    - Older lesions may show granulomatous inflammatory infiltrate
  - Sometimes curled up hair shaft is present
  - Elastic and collagen fibers may be seen, but elastic fibers are not increased (vs. EPS)
- Reactive perforating collagenosis
  - Early lesions
    - Broad, basophilic degenerated collagen layer over thin parakeratotic layer and thinned epidermis
    - Acanthosis often seen at periphery
  - Older umbilicated lesions
    - Cup-shaped central plug filled with parakeratotic debris, degenerate collagen, inflammatory cells, and debris
    - Vertically oriented collagen fibers line up and enter central plug
    - Acanthosis and hyperkeratosis at periphery
- EPS
  - Hallmark is transepidermal elimination of altered elastic tissue
    - Occurs through narrow funnel-like or "corkscrew" channel composed of eosinophilic elastin fibers and necrotic basophilic debris
    - Collarette of acanthotic, hyperkeratotic epidermis often surrounds channel
  - Base contains granulomatous chronic inflammatory infiltrate with multinucleated macrophages
  - Depending on section, altered elastin fibers may be seen streaming into channel
    - Elastic fibers are increased in size and number in subjacent papillary dermis
- Acquired perforating dermatosis

- Histopathology can take form characteristic of any primary perforating dermatoses described (especially Kyrle disease)

## ANCILLARY TESTS

### Histochemistry

- Trichrome stain
  - Can help identify altered collagen fibers in perforating collagenosis
- Verhoeff/elastin van Gieson or other elastin stains
  - Can help highlight altered elastin fibers in EPS

## DIFFERENTIAL DIAGNOSIS

### Periumbilical Perforating Pseudoxanthoma Elasticum

- a.k.a. perforating calcific elastosis and localized acquired cutaneous pseudoxanthoma elasticum
- Fragmented, clumped, calcified elastic fibers in midlower dermis extruded by transepidermal elimination (EPS noncalcified, more superficial)
- Localized plaques with peripheral keratotic papules often in striae on abdomens of obese, multiparous, African American women and sometimes history of abdominal surgery or trauma
- Very rare (~ 23 cases in literature)

### Perforating Granuloma Annulare

- Very rare disease, often on extremities of children
- Histology still shows characteristic palisading granulomas composed of necrobiotic collagen, mucin, and fibrin surrounded by lymphocytes and histiocytes
- In umbilicated lesions, granulomas were in upper dermis and extruded necrobiotic material

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

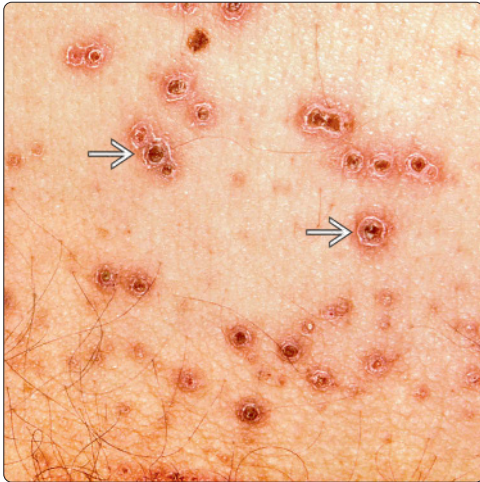
- Often, lesions show mixture of altered keratin, elastic, or collagen fibers, making histologic distinction of these diseases difficult
  - Clinical information and correlation is often necessary to establish correct diagnosis

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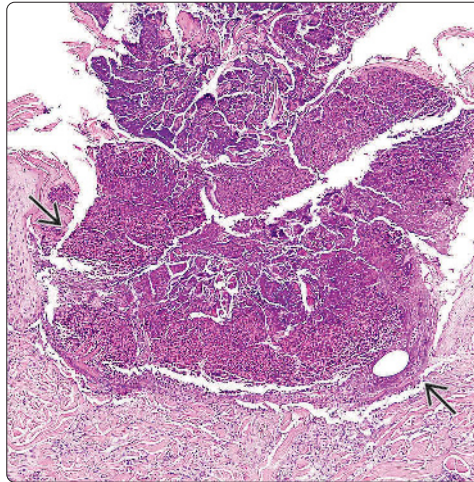
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**Keratotic Papules in Kyrle Disease**

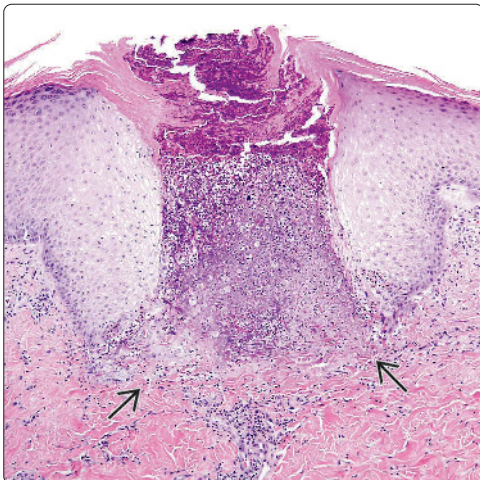


**Epidermal Invagination With Collagen Fibers**

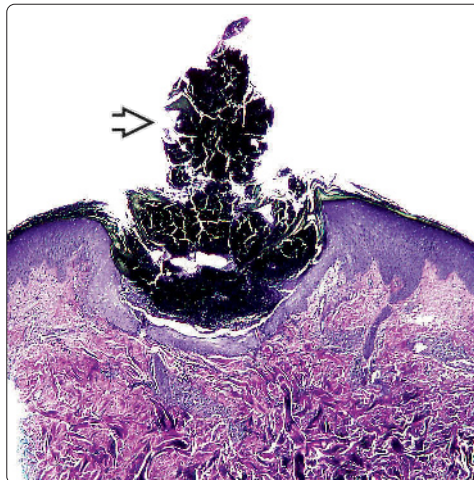


(Left) This is Kyrle disease over the chest with keratotic papules erupting through the skin and leaving chronic surrounding dull red inflammation with surrounding scale. (Right) This high-power view of reactive perforating collagenosis demonstrates a discrete epidermal invagination containing keratin, purulent material, and bright eosinophilic collagen fibers. Kyrle disease can show similar findings. (Courtesy A. Bowen, MD.)

**Transepidermal Elimination of Collagen and Elastic Fibers**

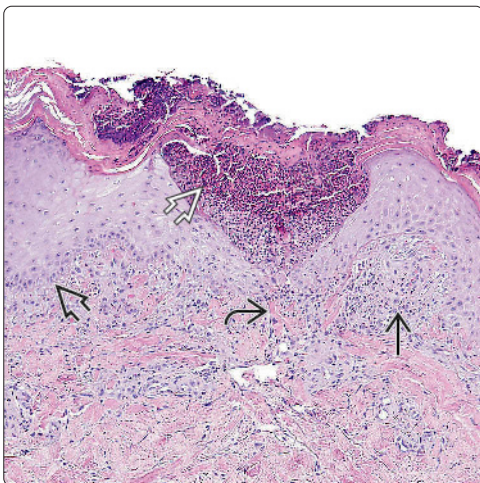


**Elimination of Black Elastin Fibers on EVG Stain**

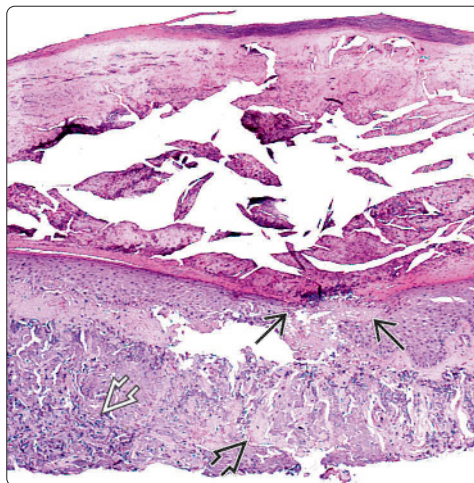


(Left) High-power view of this biopsy from a patient with an acquired perforating disorder shows a cup-shaped invagination with a plug of parakeratin with neutrophilic remnants and transepidermal elimination of collagen and elastic fibers. (Courtesy S. Florell, MD.) (Right) Elastin highlights elimination of black elastin fibers in this biopsy. This would be consistent with elastosis perforans serpiginosa.

**Transepidermal Elimination of Cellular Debris**



**Transepidermal Elimination in Perforating Granuloma Annulare**



(Left) Another example of a perforating dermatosis demonstrates acanthosis, transepidermal elimination of amorphous cellular debris with vertically oriented collagen fibers entering the debris, and a histiocytic inflammatory response. (Courtesy K. Duffy, MD.) (Right) Perforating granuloma annulare demonstrates palisading histiocytic inflammation surrounding necrobiotic collagen and mucin in the dermis with transepidermal elimination of necrobiotic material.



# Elephantiasis Nostras Verrucosa

## KEY FACTS

### TERMINOLOGY

- Massive enlargement of body part secondary to lymphedema, with associated fibrosis and hyperkeratosis

### ETIOLOGY/PATHOGENESIS

- Secondary to chronic lymphedema and usually associated with morbid obesity

### CLINICAL ISSUES

- Presents with woody induration of affected area as well as papules and nodules imparting cobblestone appearance
- Hyperkeratosis is also present
- Enlargement and disfigurement of appendage secondary to chronic lymphedema (nonfilarial)
- Typically affects legs
  - May also involve scrotum
- Almost universally arises in setting of morbid obesity
- **Treatment**

- Management is focused on treatment of venous insufficiency and lymphedema (compression)

### Prognosis

- Chronic and progressive


### MICROSCOPIC

- Hyperkeratosis
- Pseudoepitheliomatous hyperplasia
- Dome-shaped nodule formed by fibrosis in dermis with proliferation of dilated lymphatics
- Interstitial space expanded by edema

### TOP DIFFERENTIAL DIAGNOSES

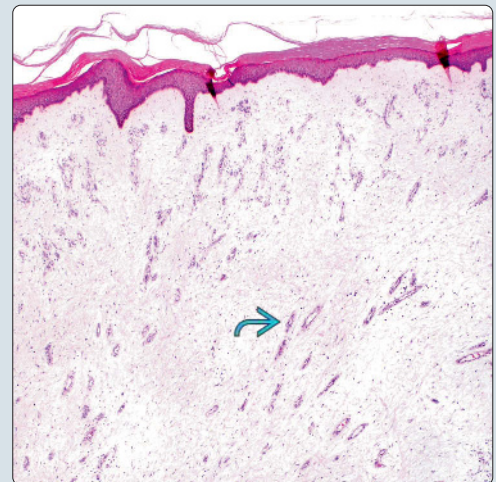
- Filarial elephantiasis
  - Occurs in absence of obesity
- Lipodermatosclerosis
  - Woody induration of legs but lacks papulonodular surface and massive hypertrophy

**Woody Induration With Cobblestone Appearance**


*(Left) Verrucous and waxy papules coalesce to form a large pebbled plaque on a leg with massive lymphedema. Fissures may occur and create a risk for cellulitis. (Right) Hyperplasia, irregular acanthosis and hyperkeratosis are seen in the epidermis. In the dermis, there is a proliferation of dermal lymphatics , which appear as thin-walled, narrow channels with a predominantly vertical orientation. Edema fluid expands the interstitial space.*

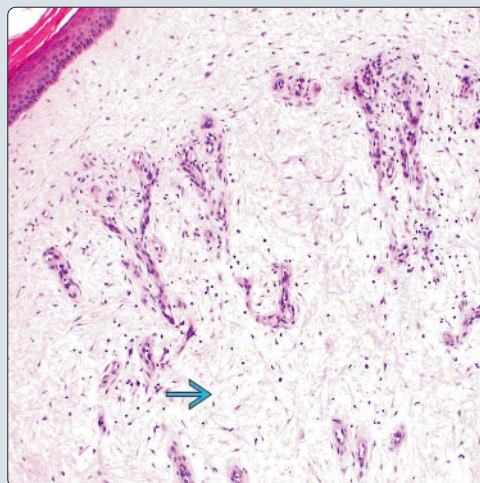


**Lymphatic Proliferation in Elephantiasis Nostras Verrucosa**

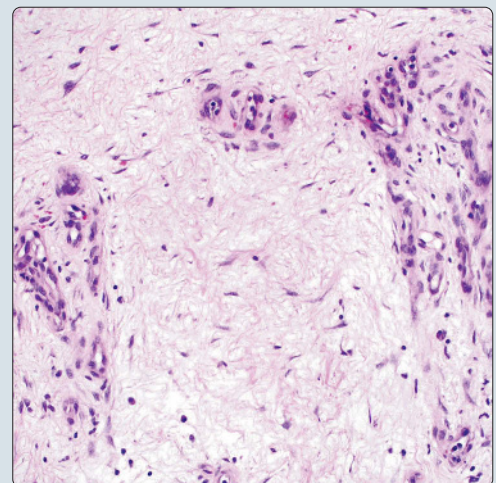


**Lymphatic Vessels With Edematous Stroma**

*(Left) Thin-walled, narrow lymphatic vessels in vertical orientation are embedded within an edematous and loose stroma . A sparse infiltrate of mononuclear cells can be seen, but the process is mostly paucinflamatory. (Right) The stroma in elephantiasis nostras verrucosa is loose and pale, expanded by edema fluid. Some spindle fibroblasts can be seen, along with sparse inflammatory cells.*



**Edematous Stroma**



## TERMINOLOGY

### Abbreviations

- Elephantiasis nostras verrucosa (ENV)

### Synonyms

- Elephantiasis nostras
- Mossy leg
- Lymphangitis recurrens elephantogenica

### Definitions

- Massive enlargement of body part secondary to lymphedema, with associated fibrosis and hyperkeratosis

## ETIOLOGY/PATHOGENESIS

### Lymphedema and Venous Stasis

- Chronic lymphedema and venous stasis are typically cause
  - Recurrent lower extremity cellulitis disrupts lymphatics and predisposes to lymphedema
  - Conversely, stasis changes can predispose to cellulitis because of epidermal breakdown
- Morbid obesity is also typically associated (almost all cases)

## CLINICAL ISSUES

### Presentation

- Enlargement and disfigurement of appendage secondary to chronic lymphedema (nonfilarial)
  - Typically affects legs
    - May also involve scrotum
  - Almost universally arises in setting of morbid obesity
  - Recurrent lower extremity cellulitis disrupts lymphatics and predisposes to lymphedema
- Presents with woody induration of affected area as well as papules and nodules imparting cobblestone appearance
  - Hyperkeratosis is also present

### Treatment

- Options, risks, complications
  - Management is focused on treatment of venous insufficiency and lymphedema (compression)
    - Since disease usually results as complication of chronic lymphedema and venous stasis
- Surgical approaches
  - Surgical debridement may be considered but wounds tend to heal poorly

### Prognosis

- Chronic and progressive
- Fissures and erosions represent portal of entry for bacterial and create a risk for cellulitis

## IMAGING

### Radiographic Findings

- Lymphoscintigraphy can aid in diagnosis of lymphedema when clinically indicated

## MICROSCOPIC

### Histologic Features

- Hyperkeratosis
- Pseudoepitheliomatous hyperplasia, irregular acanthosis

- Dome-shaped nodule formed by fibrosis in dermis with
  - Proliferation of thin-walled, narrow lymphatic channels
- Interstitial space expanded by edema
- Sparse infiltrate of mononuclear cells, but inflammation tends to be mild

## DIFFERENTIAL DIAGNOSIS

### Filarial Elephantiasis

- Caused by nematode infection
- Clinically appears identical to nonfilarial elephantiasis but may be asymmetric
  - Occurs in absence of obesity
- Typically seen in Africa and Southeast Asia

### Lipodermatosclerosis

- Panniculitis occurring in setting of chronic venous insufficiency
- Woody induration of legs
  - Lacks papulonodular surface and massive hypertrophy of ENV

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Papules and nodules formed by expanded fibrous tissue
- Dilated and proliferative lymphatic channels
- Hyperkeratosis

### Pathologic Interpretation Pearls

- Stasis-altered capillaries are small and round, while dilated lymphatics are elongated

## SELECTED REFERENCES

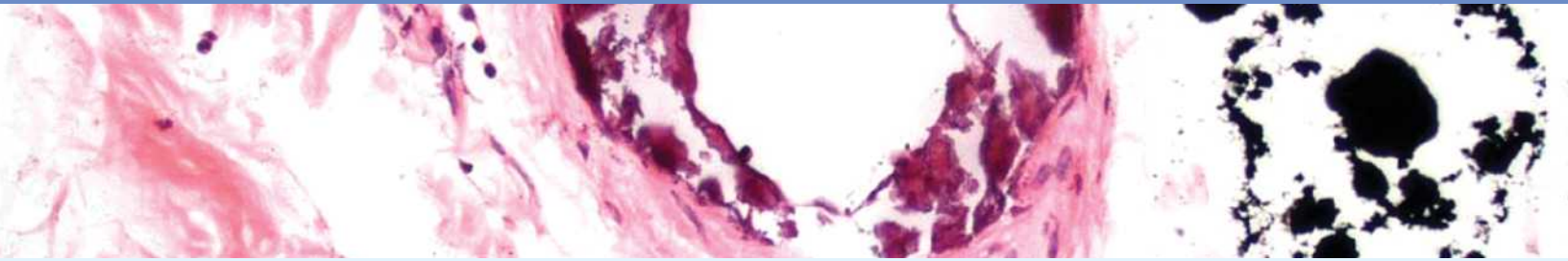
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## SECTION 8

# Metabolic/Deposition Diseases



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## Acanthosis Nigricans

## KEY FACTS

## CLINICAL ISSUES

- Presentation
  - Velvety plaques of brown skin found in intertriginous areas
  - Plaques are bilateral
  - May affect hands as well
    - Tripe palms
  - Oral mucosa may also be involved in up to 50% of cases
  - Typically no pain or pruritus
- Disease associations
  - Malignancy
    - Usually gastrointestinal, breast, pancreas, and bladder
    - Rapidly progressive and severe with widespread involvement
    - May appear with other paraneoplastic phenomena
    - Disease course tends to parallel that of underlying malignancy
  - Endocrine disorders
    - Diabetes/insulin resistance, Cushing disease, Addison disease, thyroid disorders, others
    - Hyperandrogenism, insulin resistance, and acanthosis nigricans
  - Genetic syndromes
  - Obesity

## MICROSCOPIC

- Papillomatous change of epidermis
- Hyperkeratosis with basket-weave cornified layer
- May have slight acanthosis
- Tripe palms: Acanthosis, hyperkeratosis, hypertrophy of papillary dermis

## TOP DIFFERENTIAL DIAGNOSES

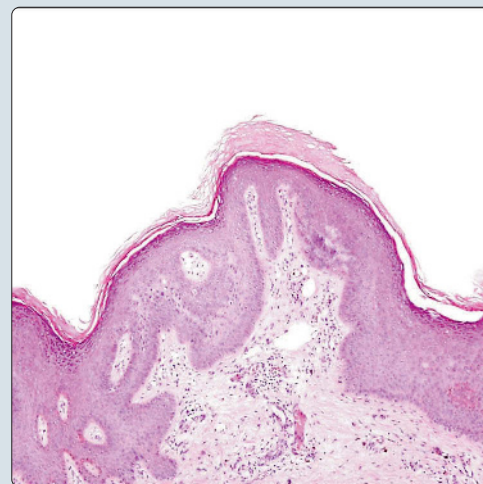
- Clinical
  - Hailey-Hailey disease
- Histopathological
  - Seborrheic keratosis, epidermal nevus

## Mild Papillomatosis

**(Left)** *Acanthosis nigricans* may have mild papillomatosis. Mild acanthosis is also present, and there is no significant inflammatory cell infiltrate. **(Right)** Papillomatosis may be more pronounced in some cases. There are overlying features of lichen simplex chronicus in this particular case.

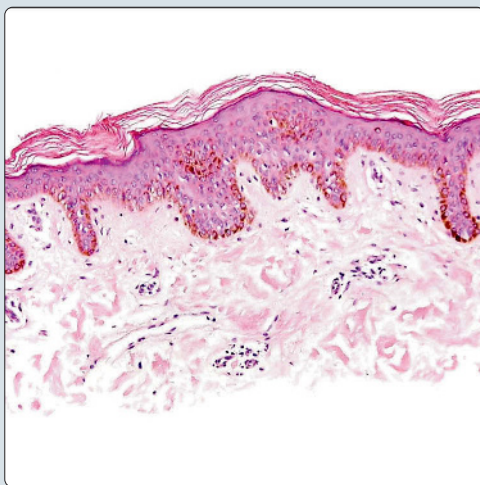


## More Pronounced Changes

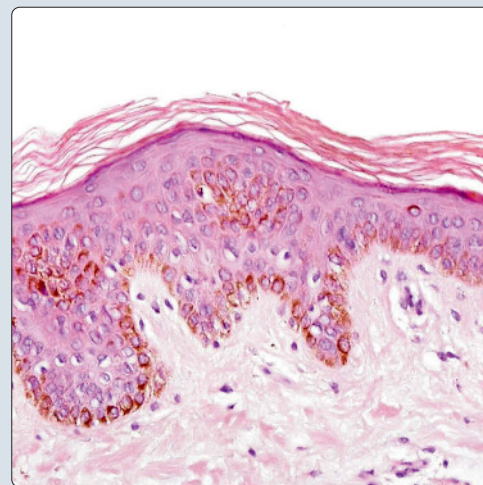


## Mild Acanthosis

**(Left)** The mild degree of acanthosis is somewhat easier to appreciate on higher power. The overlying cornified layer consists of basket-weave keratin. **(Right)** Acanthosis nigricans often displays varying degrees of hyperpigmentation as well.



## Hyperpigmentation





## TERMINOLOGY

### Definitions

- Velvety plaques of hyperpigmented skin in intertriginous areas

## CLINICAL ISSUES

### Presentation

- Velvety plaques of brown skin found in intertriginous areas
  - Most commonly nape of neck, axillae, groin
- Plaques are bilateral
- May affect hands as well
  - Usually dorsum of hands, but palms may also be affected
    - Tripe palms
- Oral mucosa may also be involved in up to 50% of cases
  - Usually not hyperpigmented
  - Deeply fissured tongue
  - Lips may have papillomatous or verrucous appearance
  - Involvement of esophagus is virtually pathognomonic for underlying gastrointestinal malignancy
- Typically no pain or pruritus

### Prognosis

- If secondary to obesity or insulin resistance, it may resolve with weight loss or resolution of diabetes
- If secondary to malignancy, it typically parallels severity of malignant tumor burden

### Disease Associations

- Malignancy
  - Usually gastrointestinal, breast, pancreas, and bladder
  - Rapidly progressive and severe with widespread involvement
  - May appear with other paraneoplastic phenomena
    - Leser-Trélat sign
    - Florid cutaneous papillomatosis
  - Disease course tends to parallel that of underlying malignancy
    - Resistant to treatment if tumor remains
- Endocrine disorders
  - Diabetes/insulin resistance, Cushing disease, Addison disease, thyroid disorders, others
  - Hyperandrogenous states, such as gigantism and acromegaly
    - May be part of HAIR-AN syndrome
      - Hyperandrogenism, insulin resistance, and acanthosis nigricans
  - Type A syndrome
    - Young women
    - Acanthosis nigricans, primary amenorrhea with hypertestosteronemia and subsequent virilization
    - Insulin resistance leading to hyperinsulinemia and hyperglycemia
      - Mutation in insulin receptors
  - Type B syndrome
    - Older patients
    - Featured by presence of autoantibodies
      - Positive for ANA, ds-DNA antibodies
      - Positive for antiinsulin receptor antibodies
      - Hypocomplementemia and proteinuria

- Elevated erythrocyte sedimentation rate

- Genetic syndromes
  - Costello syndrome, Bannayan-Riley-Ruvalcaba syndrome, Alström syndrome, and others
- Obesity
- Associated with numerous additional entities, and full discussion is beyond scope of this chapter

## MICROSCOPIC

### Histologic Features

- Skin
  - Papillomatous change of epidermis
  - Hyperkeratosis with basket-weave cornified layer
  - May have slight acanthosis
  - May have pseudohorn cysts
  - Tripe palms: Acanthosis, hyperkeratosis, hypertrophy of papillary dermis
    - Causes accentuated sulci
- Mucous membranes
  - Marked acanthosis
  - Papillomatosis of tongue
  - Hyperkeratosis with focal parakeratosis

## DIFFERENTIAL DIAGNOSIS

### Histopathological

- Seborrheic keratosis
  - Some variants have papillomatosis
  - Usually more hyperkeratosis
  - Irritated seborrheic keratosis have lymphocytic infiltrate with reactive changes in keratinocytes
  - May be indistinguishable microscopically
    - Adequate clinical history is crucial
- Epidermal nevus
  - Epidermal papillomatosis
  - Hyperkeratosis
    - May have alternating areas of orthokeratosis and parakeratosis
      - Parakeratosis predominantly over tips of papilla
  - May have lymphocytic inflammatory cell infiltrate
  - May be indistinguishable microscopically
    - Adequate clinical history is crucial

### Clinical

- Hailey-Hailey disease
  - Erythematous, hyperkeratotic plaques resulting from friction
    - Intertriginous areas
  - Skin may be cracked and weeping
  - Longitudinal bands on fingernails
  - Microscopically, there is prominent acantholysis throughout epidermis
    - Dilapidated brick wall appearance

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## KEY FACTS

### TERMINOLOGY

- Definition
  - Verrucous brown papules that preferentially occur on central chest, forming confluent reticulated pattern

### CLINICAL ISSUES

- Presents on trunk (usually central chest) as 1- to 5-mm brown to blue-gray (depending on skin type) scaly papules, coalescing into confluent plaques with areas of reticulation
- Predominantly affects dark skin types (types III-VI) but can occur on anyone
- Onset around puberty

### MICROSCOPIC

- Features can be subtle but consist of hyperkeratosis, acanthosis, and papillomatosis
- Mild, nonspecific, superficial perivascular lymphocytic infiltrate can often be seen

### TOP DIFFERENTIAL DIAGNOSES

- Acanthosis nigricans
  - Basal layer tends to be more hyperpigmented than confluent and reticulated papillomatosis
- Tinea versicolor
  - Parakeratosis and neutrophils are sometimes present
  - PAS can highlight fungal hyphae in stratum corneum
- Normal skin
  - No hyperkeratosis, or acanthosis, or hyperpigmentation
- Darier disease
  - Can appear as greasy papules or dirty, warty-appearing papules on trunk
  - Flares with heat exposures

**Brown Verrucous Papules**

(Left) Clinical photo of the central chest of a man with type IV skin shows scattered brown verrucous papules, some of which are confluent and reticulated [\[2\]](#). (Courtesy A. Lipworth, MD.) (Right) Clinical photo of the upper abdomen of a woman with type IV skin shows scattered brown verrucous papules [\[2\]](#) as well as a large plaque that demonstrates at the peripheral edge confluent and reticulated papules [\[2\]](#). (Courtesy A. Lipworth, MD.)

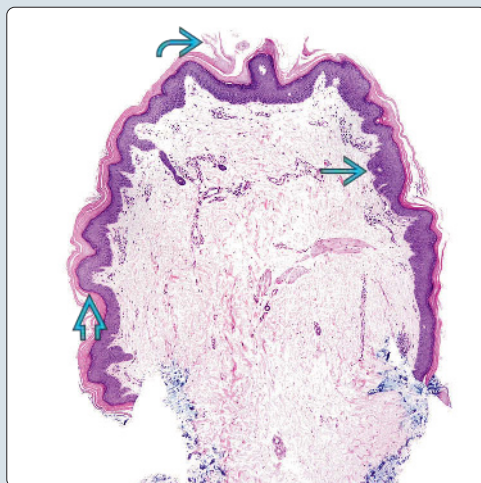


**Confluent and Reticulated Papules on Central Chest**

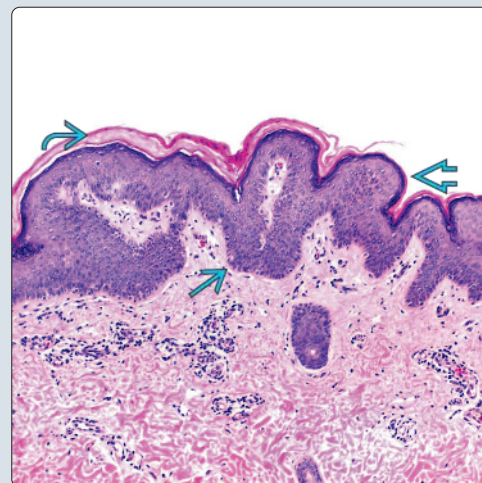


**Acanthosis, Papillomatosis, and Hyperkeratosis**

(Left) Low-power H&E of confluent and reticulated papillomatosis demonstrates mild hyperkeratosis [\[2\]](#), acanthosis [\[2\]](#), and papillomatosis [\[2\]](#). (Courtesy S. Wenson, MD.) (Right) High-power H&E of confluent and reticulated papillomatosis demonstrates mild hyperkeratosis [\[2\]](#), acanthosis [\[2\]](#), and papillomatosis [\[2\]](#). (Courtesy L. Cohen, MD.)



**Hyperkeratosis, Papillomatosis, and Acanthosis**



## TERMINOLOGY

### Abbreviations

- Confluent and reticulated papillomatosis (CARP)

### Synonyms

- CARP of Gougerot and Carteaud

### Definitions

- Verrucous brown papules that preferentially occur on central chest, forming confluent reticulated pattern

## CLINICAL ISSUES

### Epidemiology

- Age
  - Onset around puberty
- Sex
  - F > M
- Ethnicity
  - Predominantly affects dark skin types (type III-VI) but can occur on anyone

### Presentation

- Usually asymptomatic
- Presents on trunk (usually central chest) as 1- to 5-mm brown to blue-gray (depending on skin type) scaly papules, coalescing into confluent plaques with areas of reticulation

### Treatment

- Options, risks, complications
  - Treatment can be frustrating as no single agent works all of time
  - Minocycline has been reported to work ~ 1/2 of time

## MICROSCOPIC

### Histologic Features

- Features can be subtle but consists primarily of hyperkeratosis, acanthosis, and papillomatosis
- Mild, nonspecific, superficial perivascular lymphocytic infiltrate can often be seen

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Acanthosis nigricans
  - Basal layer tends to be more hyperpigmented than CARP
- Tinea versicolor
  - Parakeratosis and neutrophils are sometimes present
  - PAS can highlight fungal hyphae in stratum corneum
- Normal skin
  - No hyperkeratosis, acanthosis, or hyperpigmentation
  - Dermal papillae and epidermal rete ridges are uniform in appearance
  - PAS stain would be negative for fungal hyphae

### Clinical

- Acanthosis nigricans
  - More velvety in texture, preferentially affects skin folds (neck, axilla, groin), associated with systemic disease or malignancy
- Tinea versicolor

- More common in humid climates, as it tends to wax and wane in course, often leaving scaly hypopigmented macules, patches due to production of azelaic acid
- Positive hyphae on KOH or PAS (although biopsies usually not necessary)
- Darier disease
  - Can appear as greasy papules or dirty, warty-appearing papules on trunk
  - Flares with heat exposures
  - Palmar pits, longitudinal ridging, distal nail triangular defects, occasionally white mucosal plaques in mouth

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Reticulated and confluent brown to blue-gray scaly papules on trunk of dark-skinned individuals

### Pathologic Interpretation Pearls

- Features can be subtle but consists primarily of hyperkeratosis, acanthosis, and papillomatosis

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# Amyloidosis

## KEY FACTS

### CLINICAL ISSUES

- Systemic amyloidosis (SA): Nonpruritic, waxy papules on scalp, neck, and, face with predilection for periorbital area and plaque-like lesions on hands and flexural areas
- Macular amyloidosis (MA): Pruritic, vaguely defined, rippled brown macules ("hammered brass"), often on back and interscapular region
- Lichen amyloidosis (LA): Small, occasionally pruritic, waxy papules and lichenified plaques, often on extensor surfaces of lower extremities (shins)
- Nodular amyloidosis (NA): Single or numerous large, waxy nodules on lower extremities, face, neck, scalp, or genitalia

### MICROSCOPIC

- Systemic amyloidosis
  - Amyloid in dermis, subcutis, and walls of vessels
- Macular, lichen, biphasic amyloidosis
  - Papillary dermis contains small eosinophilic globules of amyloid that can be subtle

- Epidermis contains apoptotic bodies and basal vacuolar change
- Perivascular chronic inflammatory cell infiltrate is typically present
- Nodular amyloidosis
  - Dermis and subcutis contain large masses of amyloid focused around vessels and adnexa
  - Monoclonal plasma cells with Russell bodies
  - Deposition of amyloid light chain has been shown in many cases

### ANCILLARY TESTS

- Immunohistochemistry is superior to other ancillary detection methods

### TOP DIFFERENTIAL DIAGNOSES

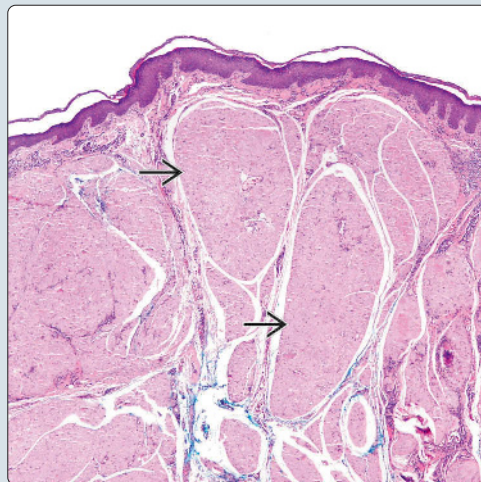
- Porphyria
- Adult colloid milium
- Lipoid proteinosis

Waxy Indurated Papules

(Left) In this image, amyloidosis is demonstrated by waxy indurated papules on the eyelids. There is also a shave biopsy site on the right upper eyelid, which confirmed the diagnosis. (Right) Amyloid is an amorphous, acellular, eosinophilic substance as seen on H&E section in this case of nodular amyloidosis.

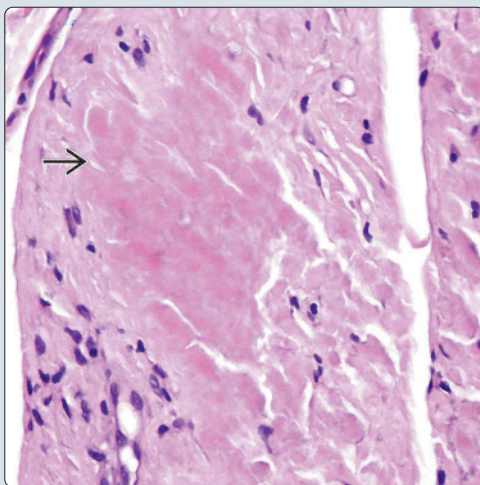


Amorphous Acellular Eosinophilic Material



Amorphous, Acellular Eosinophilic Substance

(Left) Amyloid is an amorphous, acellular, eosinophilic substance on H&E sections. (Right) The histopathologic diagnosis of macular amyloidosis (MA) can easily be missed by both clinician and pathologist. The differential diagnosis includes other entities that can appear normal from low power. Subtle eosinophilic amorphous material can be seen in this biopsy of MA.



Eosinophilic Globules in Papillary Dermis



## TERMINOLOGY

### Definitions

- Generic term denoting extracellular tissue deposition of eosinophilic fibrils composed of altered autologous proteins

## ETIOLOGY/PATHOGENESIS

### 6 Important Amyloid Proteins in Cutaneous Pathology

- Amyloid light chain (AL) is derived from immunoglobulin light chains
- Amyloid A protein (AA) is HDL3-associated lipoprotein and acute phase reactant
- Amyloid transthyretin protein is present in certain heritable amyloidosis syndromes
- A $\beta$ -2-microglobulin protein induced by  $\beta$ -2-microglobulin glycosylated polypeptide
- Amyloid keratin protein (AK) in primary cutaneous amyloidosis derived from filamentous degeneration of keratin filaments

### Systemic Amyloidosis

- Primary systemic amyloidosis (SA); often involves skin
  - Deposition of AL (kappa or lambda)
  - May be multiple myeloma (MM) associated
  - Occurs in ~ 1/3 of patients with MM
- Secondary SA
  - Usually no skin involvement
  - Deposition of AA, amyloid A, or derived from  $\beta$ -2-microglobulin following long-term hemodialysis
- Heritable amyloidosis
  - Includes entities such as familial Mediterranean fever, Muckle-Wells syndrome, familial cold autoinflammatory syndrome, and familial amyloidotic polyneuropathy
- Amyloid elastosis
  - Rare entity with cutaneous lesions and progressive systemic disease

### Primary Localized Cutaneous Amyloidosis

- Macular amyloidosis (MA)
  - Deposition of AK, amyloid keratin protein, which is keratin intermediate filament
- Lichen amyloidosis (LA)
  - Deposition of AK, which is keratin intermediate filament
- Nodular amyloidosis (NA)
  - Deposition of AL has been shown in many cases
- Poikilodermatous amyloidosis
  - Rare form of localized cutaneous amyloidosis
- Anosacral amyloidosis
  - Rare form of localized cutaneous amyloidosis

## CLINICAL ISSUES

### Epidemiology

- Age
  - Primary localized cutaneous amyloidosis (PLCA): Predominantly adult population with earliest cases appearing around puberty
- Sex
  - MA: Affects females more than males

- LA: Affects sexes equally
- Ethnicity
  - SA: In developed countries, AL is most frequently deposited precursor protein, whereas, in developing countries, AA is most frequently deposited precursor protein
  - MA: Seen with increased frequency in patients from Middle East, Asia, and Central and South America
  - LA: Seen with increased frequency in patients from Southeast Asia

### Presentation

- Variable depending on organ affected, amount of amyloid deposited, and type of precursor protein
- Systemic amyloidosis
  - Major sites of clinically important involvement include kidneys, heart, skin, and liver
  - Cutaneous manifestations include
    - Subcutaneous nodules or plaques on hands and flexural areas
    - Waxy thickening on scalp, face, and neck
    - Easy bruising of lesions
    - Commonly hemorrhage secondary to amyloid depositing within blood vessel walls resulting in increased fragility
- PLCA
  - MA
    - Pruritic, vaguely defined, rippled brown macules ("hammered brass"), often on back and interscapular region
  - LA
    - Small, occasionally pruritic, waxy papules and lichenified plaques, often on extensor surfaces of lower extremities (shins)
  - NA
    - Single or numerous large, waxy nodules on lower extremities, face, neck, scalp, or genitalia
  - Poikilodermatous amyloidosis
    - Poikilodermatous skin lesions and lichenoid papules
    - Associated with photosensitivity, short stature, and palmoplantar keratoderma
  - Anosacral amyloidosis
    - Lichenoid papules and scaly hyperpigmented macules in perianal region

### Laboratory Tests

- Diagnosis can be made by tissue biopsy; this is important for determining, rather than assuming, deposited precursor protein
  - SA without obvious skin lesions: Blind biopsy of salivary gland, abdominal fat, or rectum

## MICROSCOPIC

### Histologic Features

- Amorphous and eosinophilic with hematoxylin and eosin stains
- Cutaneous findings in systemic amyloidosis
  - Papules are created by deposits in papillary dermis, can attenuate overlying epidermis if large and show clefting in and around amyloid
  - Plaques show diffuse involvement and amyloid

- Extends into subcutaneous layer forming rings around individual adipocytes
- Concentrates around blood vessels
- Can involve pilosebaceous units, causing follicular atrophy and alopecia
- Bullous lesions are uncommon but demonstrate intradermal cleavage within amyloid deposits
- No pigmented cells, scarce inflammatory cells, and, in contrast to localized cutaneous forms, no epidermal involvement
- Clinically normal skin demonstrates histological deposition of amyloid in 50% of patients
- Amyloid elastosis
  - Deposition of amyloid surrounding elastic microfibrils of skin and serosa
- Macular, lichenoid, and biphasic amyloidosis (clinical variants of same process)
  - Papillary dermis contains small eosinophilic globules of amyloid that can be subtle
  - Epidermis contains apoptotic bodies and basal vacuolar change
  - Perivascular chronic inflammatory cell infiltrate is typically present
  - LA may resemble lichen simplex chronicus with hyperkeratosis and acanthosis of overlying epidermis
  - In contrast to systemic amyloidosis, no amyloid deposition around blood vessels
- NA
  - Dermis and subcutis contain large masses of amyloid, concentrating around blood vessels and adnexa
    - These regions do not stain with antikeratin antibodies, may stain for  $\lambda$ ,  $\kappa$ , or  $\beta$ -2-microglobulin
  - Monoclonal plasma cells with Russell bodies present
  - Foreign body giant cells and focal calcification are viewed on occasion
- Poikilodermatous amyloidosis
  - Dermal papilla contain amyloid, concentrating around blood vessels

## ANCILLARY TESTS

### Immunohistochemistry

- Monoclonal antibody EKH4, keratin antibody AE1, and anti-keratin antibody 34bE12 stain amyloid in MA and LA
- Antisera available against AA, AL,  $\kappa$ ,  $\lambda$ , and  $\text{A}\beta$ -2 microglobulin
- Serum amyloid protein, does not discriminate between types of amyloid
  - Nonfibrillar glycoprotein, which binds to any subtype of amyloid fibril

### Immunofluorescence

- IgM and C3 complement have been seen in localized cutaneous forms of amyloidosis

### Electron Microscopy

- Fibrils are 6-10 nm in width, indefinite length, straight, unbranching, and haphazardly arranged
- Demonstrates hollow core on cross sectioning
- Associated with elastic fibers and lack cross banding of collagen

## Detection of Amyloid

- Congo red, producing apple-green birefringence under polarized light
  - Pretreatment of sections with potassium permanganate prevents staining of secondary systemic amyloidosis (AA) while retaining staining of AL
- Thioflavine T
  - Intense yellow-green fluorescence
- Crystal violet and methyl violet: Metachromatic staining
- Pagoda red no. 9 (Dylon)
  - Variant of Congo red, more specific for amyloid than Congo red, as it does not stain lipid proteinosis, colloid milium, or solar elastosis
  - Apple-green birefringence under polarized light
- Scarlet red (RIT)
- Hematoxylin and eosin: Pink staining

## DIFFERENTIAL DIAGNOSIS

### Diseases With Amorphous Pink Material

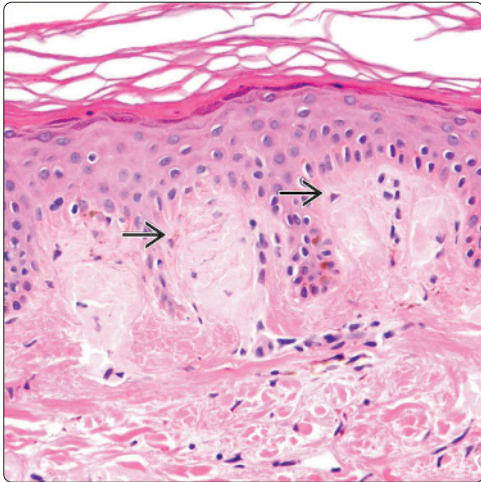
- Porphyria
  - Lightly eosinophilic hyaline material that is PAS positive and diastase resistant is seen in and around vessels
  - Subepidermal blisters with festooning of dermal papillae
  - Eosinophilic material is negative for all other stains typically positive in amyloid
- Adult colloid milium
  - Severely degenerated elastic fibers in large sheets in papillary and reticular dermis without inflammation and many cracks and fissuring
    - Solar elastosis is invariably present, and grenz zone of normal collagen is typically present
  - Hyaline material is very similar in appearance and staining patterns to amyloid
  - Colloid is negative with methyl violet and pagoda red no. 9 stains and has no apple-green birefringence
- Lipoid proteinosis
  - Hyaline deposits around dermal blood vessels (in onion skin pattern) and eccrine glands are also PAS positive and diastase resistant
  - Material is only weakly positive with Congo red and methyl violet and negative with pagoda red no. 9
  - Material positive with colloidal iron, Alcian blue, Sudan black, and oil red O (all negative for amyloid)
- Waldenström macroglobulinemia
  - PAS-positive, diastase-resistant eosinophilic amorphous material uncommonly can be seen in skin
  - Material is strongly reactive with IgM antibody and negative with other typical amyloid stains

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**Eosinophilic Globules in Papillary Dermis**



**Gray Hyperpigmentation and Vague Brown Macules**

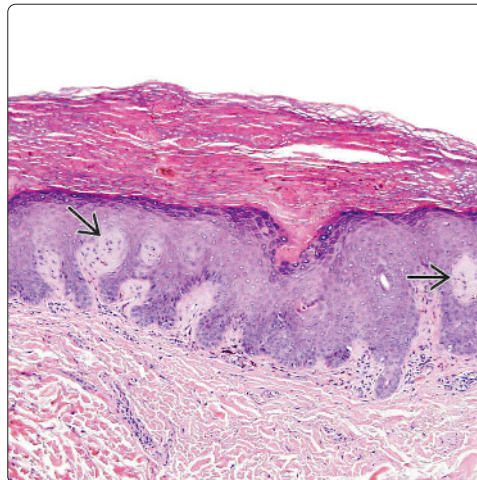


(Left) MA is illustrated by the presence of subtle eosinophilic globules of amyloid in the papillary dermis. A Congo red or other amyloid stains can help highlight the amyloid in difficult cases. (Right) MA is seen on the back, which is a classic location. There is gray hyperpigmentation and vaguely defined brown macules. A biopsy site is seen on the left upper back.

**Lichenoid Brown-Purple Waxy Papules and Plaques**

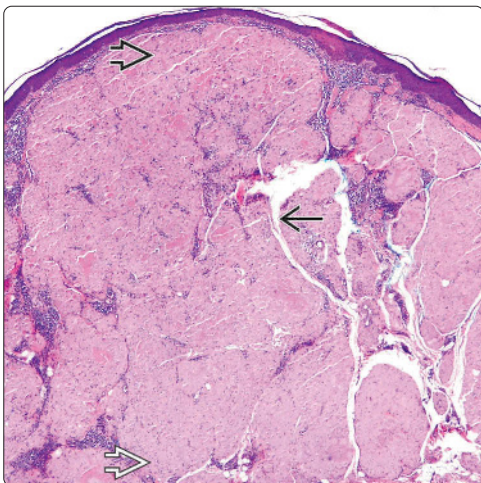


**Eosinophilic Papillary Dermal Globules With Hyperkeratosis**

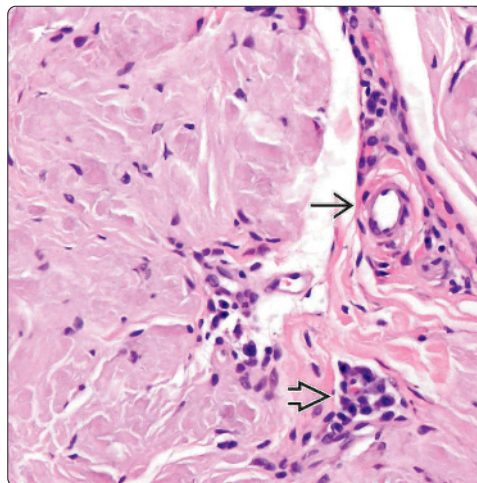


(Left) Lichen amyloidosis (LA) shows lichenoid, brown-purple, waxy papules and plaques over the knee. These lesions are classically seen on extensor surfaces. (Right) There are many histologic similarities between MA and LA. In this specimen of LA, the vaguely defined eosinophilic globules can be seen in the papillary dermis. Clinical correlation can be helpful, as LA is typically papules and MA is typically macules. (Courtesy S. Florell, MD.)

**Nodules of Amyloid Deposition in Dermis**



**Concentration Around Blood Vessels and Plasma Cells**



(Left) Nodular amyloidosis is characterized by large deposits of amyloid in the dermis and subcutis of the skin. Fissures usually develop within the amyloid. (Right) Nodular amyloidosis is known to concentrate around blood vessels. It is common to see plasma cells within the large regions of amyloid or clustered with higher concentrations at the margins of a lesion.



## Colloid Milium

## KEY FACTS

## TERMINOLOGY

- Colloid degeneration of skin, paracolloid, miliary colloidoma
- Presence of multiple dome-shaped, skin-colored to yellow-orange or white papules on sun-exposed skin, most frequently involving the face

## CLINICAL ISSUES

- There are primarily adult and juvenile types, both of which present as asymptomatic dome-shaped, skin-colored to yellow-orange or white papules on sun-exposed skin on face

## MICROSCOPIC

- Nodules of amorphous colloid material within papillary dermis often with clefting and fissures
  - Grenz zone more prominent in adult onset
  - Juvenile form with less clefting and fissures
- Pigmented variant

- Similar to adult onset type but with light pigmentation of dermal papillary nodules

## TOP DIFFERENTIAL DIAGNOSES

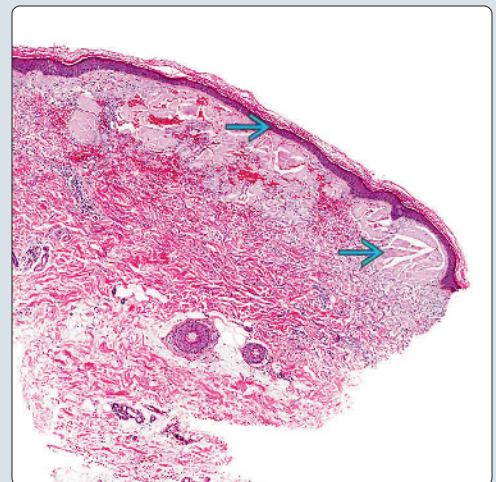
- Systemic amyloidosis
  - May have more prominent dermal involvement than papular nature of colloid milium
  - Systemic symptoms with stigmata (macroglossia, purpura, carpal tunnel syndrome)
- Lipoid proteinosis
  - PAS(+) but Congo red and thioflavin T (-)
  - Recurrent blistering episodes, waxy yellow papules and skin thickening, hoarse throat
- Papular mucinosis
  - Mucin deposition is present in dermis
  - More localized presentation of waxy firm papules without any systemic features

## Yellow-Orange Confluent Papules

(Left) Yellow-orange confluent papules on the forehead of a man with chronic sun damage are shown. The biopsy showed colloid milium. (Right) Low-power H&E demonstrating subtle aggregates of colloid material within the papillary dermis.



## Aggregates of Colloid Material in Papillary Dermis

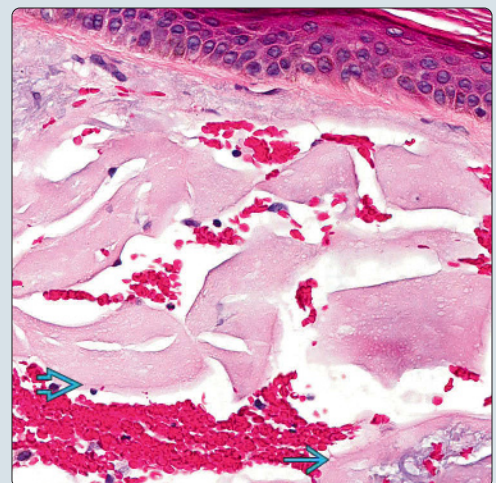


## Papillary Dermis With Colloid Aggregates

(Left) Medium-power H&E demonstrates the clefting and fissuring of the colloid material within the papillary dermis. (Right) High-power H&E demonstrates the clefting and fissuring of the colloid material within the papillary dermis.



## Clefting and Fissuring



**TERMINOLOGY****Synonyms**

- Colloid degeneration of skin, paracolloid, miliary colloidoma

**Definitions**

- Presence of multiple dome-shaped, skin-colored to yellow-orange or white papules on sun-exposed skin, most frequently involving the face

**CLINICAL ISSUES****Presentation**

- There are primarily adult and juvenile types, both of which present as asymptomatic, dome-shaped, skin-colored to yellow-orange or white papules on sun-exposed skin
  - Adult onset (most common)
    - Primarily affected middle-aged men with histories of excessive sun exposure and fair skin
  - Juvenile form
    - Similar presentation as in adult form but appears before puberty
    - Can be autosomal recessive or dominant in nature
- Less commonly, there is pigmented form thought to be secondary to excessive use of bleaching agents (hydroquinone)

**Treatment**

- Options, risks, complications
  - Resurfacing lasers, retinoids, chemical peels, or cryotherapy

**MICROSCOPIC****Histologic Features**

- Adult onset
  - Grenz zone is typically present
  - Nodules of amorphous colloid material within papillary dermis often with clefting and fissures
  - Background of dermal solar elastosis is often present
- Juvenile form
  - Grenz zone is typically **not** present
  - Nodules of amorphous colloid material within papillary dermis often with less clefting and fissures than in adult form
  - Characteristic feature is keratinocyte apoptosis in overlying epidermis
- Pigmented variant
  - Similar to adult-onset type but with light pigmentation of dermal papillary nodules

**ANCILLARY TESTS****Histochemistry**

- Adult onset
  - Similar to amyloidosis with PAS, thioflavin T, Congo red, and crystal violet (+)
- Juvenile form
  - Stains positive with keratins

**DIFFERENTIAL DIAGNOSIS****Histopathologic**

- Systemic amyloidosis
  - May have more prominent dermal involvement than papular nature of colloid milium
- Lipoid proteinosis
  - PAS(+) but Congo red and thioflavin T (-)
  - ECM1 immunohistochemistry may help
- Papular mucinosis
  - Mucin deposition is present in dermis

**Clinical**

- Systemic amyloidosis
  - Systemic symptoms with stigmata (macroglossia, purpura, carpal tunnel syndrome)
- Lipoid proteinosis
  - Recurrent blistering episodes, waxy yellow papules and skin thickening, hoarse throat
- Papular mucinosis
  - More localized presentation of waxy firm papules without any systemic features

**DIAGNOSTIC CHECKLIST****Clinically Relevant Pathologic Features**

- There are primarily adult and juvenile types, both of which present as asymptomatic, dome-shaped, skin-colored to yellow-orange or white papules on sun-exposed skin

**Pathologic Interpretation Pearls**

- Nodules of amorphous colloid material within the papillary dermis often with clefting and fissures
  - Grenz zone more prominent in adult onset
  - Juvenile form with less clefting and fissures

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## Calcinosis Cutis

## KEY FACTS

## TERMINOLOGY

- Benign deposition of insoluble calcium deposits in skin and subcutaneous tissues in response to tissue damage or metabolic derangements

## CLINICAL ISSUES

- Multiple white, firm papules, plaques, or nodules that may be asymptomatic or tender and may impinge upon adjacent structures or ulcerate
- 5 subtypes with varying distributions
- Calciophylaxis has poor prognosis, related to underlying condition as well as extent of necrosis and resulting amputation
- Juvenile dermatomyositis has better overall prognosis but higher incidence of calcinosis cutis compared with adult dermatomyositis

## MICROSCOPIC

- Fine granules or nodules of crystalline or amorphous calcium within dermis or subcutaneous tissue

- Calcium stains dark blue with H&E
- Precipitated calcium often promotes foreign body reaction characterized by histiocytes and multinucleated giant cells
- Calciophylaxis is characterized by calcification of capillary-sized vessels
- Atherosclerotic calcification of larger vessels is often present as well


## ANCILLARY TESTS

- von Kossa stains calcium black
- Alizarin red S stains calcium red

## TOP DIFFERENTIAL DIAGNOSES

- Eruptive xanthoma
- Gout
- Oxalosis

**Yellowish-White Calcium Deposits from Exposure to Calcium Salt**



(Left) *Calcinosis cutis secondary to topical exposure to a calcium salt is shown. The dermal calcium deposits appear yellowish-white*  *because of carotenoids in the overlying epithelium and within histiocytes. (Right)* *Tumoral calcinosis typically involves periarticular tissue and is often familial.*

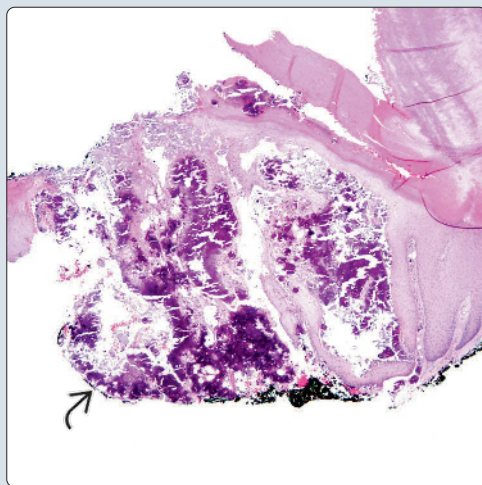


**Large Calcium Deposits of Tumoral Calcinosis**

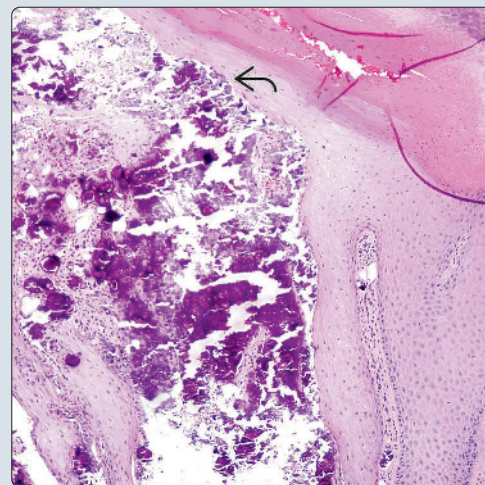


**Calcinosis Cutis Secondary to Trauma (Heel Stick)**

(Left) *Subepidermal calcified nodule*  *occurs on the chin of a child or at the site of the heel stick in an infant. (Right)* *Higher-power view of subepidermal calcified nodule demonstrates transepidermal elimination of calcium* .



**Transepidermal Elimination of Calcium**



**TERMINOLOGY****Abbreviations**

- Calcinosis cutis (CC)

**Definitions**

- Benign deposition of insoluble calcium deposits in skin and subcutaneous tissues in response to tissue damage or metabolic derangements

**ETIOLOGY/PATHOGENESIS****Environmental Exposure**

- Dystrophic CC occurs at sites of tissue damage
  - Serum levels of calcium and phosphate are usually normal
  - Tissue damage causes calcium influx, elevating intracellular calcium concentration and creating an acidic environment that interferes with inhibitors of calcification
  - Denatured proteins from necrotic cells bind phosphate, serving as a nidus for calcium crystal formation
  - Intracellular calcium precipitates within tissues as crystals of hydroxyapatite or amorphous calcium phosphate

**Metabolic Derangements**

- Metastatic CC involves calcification of normal tissue because of elevations of serum calcium and phosphate
  - Hypercalcemia and hyperphosphatemia cause CC when  $> 70 \text{ mg}^2/\text{dL}^2$  is present extracellularly, elevating intracellular concentration to a point where CC can occur
  - Elevations are commonly related to renal disease, although they can also be caused by infusion of calcium or topical exposure to calcium salts
  - Calciophylaxis is a form of metastatic CC characterized by rapid, widespread calcification of capillary-sized vessels resulting in retiform tissue necrosis

**Disease Associations**

- Dystrophic CC is commonly related to
  - Scleroderma
  - CREST syndrome (CC, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia)
  - Systemic lupus erythematosus
  - Porphyria cutanea tarda
  - Dermatomyositis
  - Pseudoxanthoma elasticum
  - Werner syndrome
  - Ehlers-Danlos syndrome
  - Cutaneous neoplasms
  - Milk alkali syndrome
  - Hypervitaminosis D
  - End-stage renal disease
- Metastatic CC associated with systemic disease typically relates to chronic kidney disease
- Calciophylaxis
  - End-stage kidney disease secondary to diabetes mellitus is usual setting
  - Other possible causes include
    - Rapid weight loss
    - Renal transplantation

- Other causes of hyperparathyroidism
- Functional protein C and protein S deficiency
- Nonuremic calciophylaxis has been reported in settings of
  - Malignancy
  - Alcoholic liver disease
  - Connective tissue disease
- Preceding corticosteroid use is noted in  $> 1/2$  of patients with nonuremic calciophylaxis
  - Protein C and S deficiencies are noted in  $\sim 11\%$  of patients

**CLINICAL ISSUES****Epidemiology**

- Age
  - Children more often present with subepidermal calcified nodules (an idiopathic form of CC characterized by transepidermal elimination of calcium)
  - Tumoral CC and CC universalis presents between ages 10-30
  - CC circumscripta arises during middle age
  - Idiopathic scrotal CC occurs in older men and results from calcification of scrotal epidermoid cysts
- Sex
  - No predilection has been demonstrated
- Ethnicity
  - Tumoral calcinosis is a dramatic form of CC that presents more commonly in black South Africans

**Presentation**

- Multiple white, firm papules, plaques, or nodules that may be asymptomatic or tender and may impinge upon adjacent structures or ulcerate
- Chalky white material may be visible within lesions
- 5 subtypes with varying distributions
- Dystrophic CC
  - Most common subtype, generally localized to an area of tissue damage or abnormality exposed to repetitive microtrauma (connective tissue disease, trauma, neoplasm, infection)
  - Serum calcium and phosphate are normal
- Metastatic CC
  - Widespread deposition, commonly periarticular (knees, elbows, and shoulders), but may be visceral
  - Results from metabolic abnormalities: Serum calcium and phosphate are elevated
- Idiopathic CC
  - Localized to 1 area with normal serum calcium and phosphate levels
  - Includes
    - Idiopathic scrotal calcinosis in older males
    - Subepidermal calcified nodule, which occurs around chin of a child
- Iatrogenic CC
  - Follows procedures such as
    - Liver transplant
    - Use of calcium chloride electrode paste
    - Treatment with IV calcium gluconate or para-aminosalicylic acid
- Calciophylaxis

- Small vessel vasculopathy occurring in dermis and subcutaneous fat
  - Presents with retiform necrosis of fatty areas such as abdomen, breast, or thigh
  - Ischemic pain is often dramatic, and resulting necrosis may progress rapidly, necessitating amputation

### Treatment

- Options, risks, complications
  - No standard treatment for CC
  - For calciphylaxis
    - Control of calcium and phosphate levels, debridement, and treatment of associated infection and metabolic disturbances
    - Rapid relief of pain and cessation of progression have been noted with sodium thiosulfate infusion
    - Tissue plasminogen activator (tPA) therapy has also been used with anecdotal success
- Surgical approaches
  - Localized disease often responds best to simple curettage
  - Other surgical modalities include excision, carbon dioxide laser, and extracorporeal shock wave lithotripsy
- Drugs
  - Variable and limited success reported with
    - Intralesional corticosteroids
    - Minocycline
    - Ceftriaxone
    - Magnesium and aluminum antacids
    - Bisphosphonates
    - Myo-inositol hexaphosphonate
    - Probenecid
    - Colchicine
    - Warfarin
    - Diltiazem
    - Sodium thiosulfate
    - Intravenous immunoglobulin

### Prognosis

- Parallels prognosis of underlying cause
- Juvenile dermatomyositis has better overall prognosis but higher incidence of CC, compared with adult dermatomyositis
- Calciphylaxis has poor prognosis, related to underlying condition as well as extent of necrosis that may necessitate amputation

## MICROSCOPIC

### Histologic Features

- Fine granules or nodules of crystalline or amorphous calcium within dermis or subcutaneous tissue
  - Calcium stains dark blue with H&E
- Precipitated calcium often promotes a foreign body reaction characterized by histiocytes and multinucleated giant cells
- Chronic inflammation results in fibrosis
- Calciphylaxis is characterized by calcification of capillary-sized vessels
  - Atherosclerotic calcification of larger vessels is often present as well

## ANCILLARY TESTS

### Histochemistry

- von Kossa
  - Stains calcium black
- Alizarin red S
  - Stains calcium red

## DIFFERENTIAL DIAGNOSIS

### Histopathological

- Eruptive xanthoma
  - Demonstrates crystalline extracellular lipid surrounded by histiocytes
  - Presence of surrounding xanthoma cells and amphophilic crystalline nature of deposits suggests correct diagnosis
- Gout
  - Demonstrates feathery urate crystals surrounded by multinucleated giant cells and histiocytes
  - In formalin-fixed tissue, crystals appear more amorphous, but feathery pattern is preserved toward center of deposits and amphophilic color is characteristic
- Oxalosis
  - Presents with birefringent clover leaf-shaped crystals in skin
  - Deposits stain poorly but refract light strongly

### Clinical

- Molluscum contagiosum
  - Fleshy, pink, umbilicated papules
- Milia
  - Small white inclusion cysts, related to cutaneous adnexa
  - Commonly present on face, neck, or hands
- Mycetoma
  - Chronic plaque with draining sinus tracts that spit out fungal or bacterial grains
- Osteoma cutis
  - Area of ossification related to tissue damage or tumor
  - Miliary osteomas occur in old acne scars
- Xanthomas
  - Yellow deposits of xanthoma cells, typically in setting of hyperlipidemia
  - Commonly involve extensor surfaces
    - Xanthelasma involves eyelid

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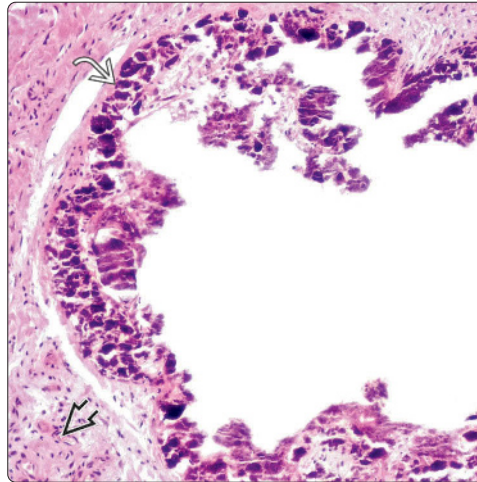
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


**Small, Yellow Calcifications in Scrotal Calcinosis**



**Nodular Calcium Deposits in Scrotal Calcinosis**



**(Left)** Idiopathic scrotal calcinosis occurs in older males and represents calcification of scrotal epidermoid cysts. **(Right)** Idiopathic scrotal calcinosis is characterized by nodular deposits of calcium . The surrounding tissue demonstrates many small bundles of smooth muscle , characteristic of genital skin.

**Extensive Cutaneous Necrosis From Calciophylaxis**



**Calcified Vessel in Calciophylaxis**

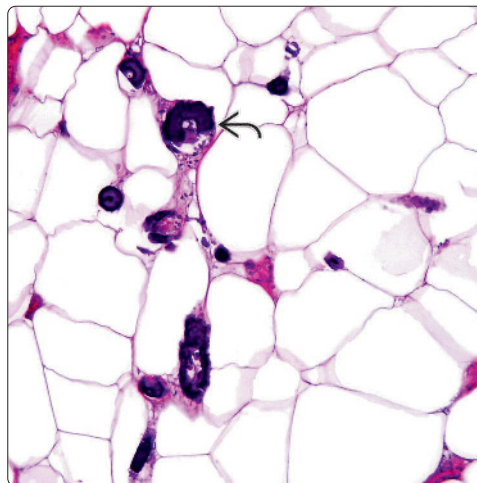



**(Left)** This is the breast demonstrating extensive cutaneous ischemia and necrosis from a patient with calciophylaxis. **(Right)** This is a high-power view of a calcified capillary-sized vessel in the subcutis in a case of calciophylaxis.

**Ischemic Necrosis From Calciophylaxis**



**Multiple Calcified Capillary-Sized Vessels**



**(Left)** Calciophylaxis results in extensive ischemic necrosis of tissue and often results in amputation and death. **(Right)** Calciophylaxis is characterized by calcification of capillary-sized vessels .

## Osteoma Cutis

## KEY FACTS

## TERMINOLOGY

- Benign osseous tissue in dermis or subcutis
- Strictest definition is **primary** ossification of cutaneous tissue
  - As opposed to secondary calcification arising due to preceding inflammatory, neoplastic or traumatic insult
- May present sporadically, as miliary osteomas of face or as part of genetic syndrome
  - Genetic syndromes include
    - Albright hereditary osteodystrophy
    - Progressive osseous heteroplasia
    - Plate-like osteoma cutis

## CLINICAL ISSUES

- Single or multiple firm dermal papules, plaques, or subcutaneous nodules
- Osteomas may be single or multiple
- Albright hereditary osteodystrophy should be investigated when presenting early in life

## MICROSCOPIC

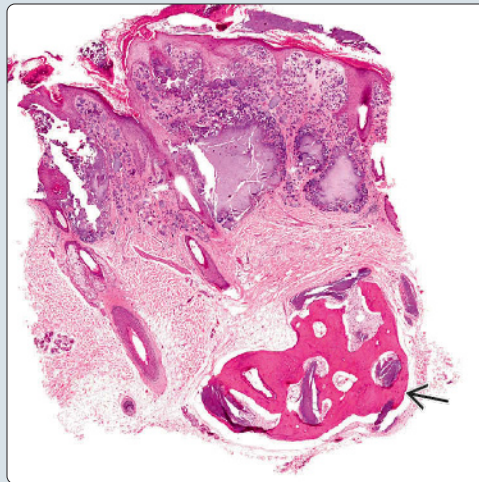
- Mature lamellar bone within dermis or subcutis
- Marrow spaces may be present
- Osteoblasts may be present

## TOP DIFFERENTIAL DIAGNOSES

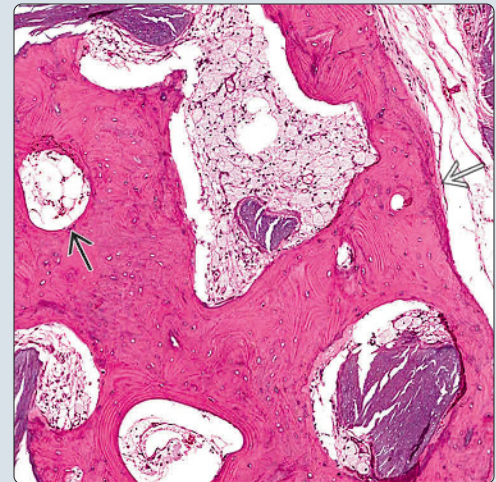
- Osteochondroma
  - Mature cartilage with layer of lamellar bone
- Extraskelatal osteosarcoma
  - Ill-defined with pleomorphic cells
- Secondary ossification
  - Can be due to a variety of stimuli such as
    - Inflammation
    - Neoplasms
    - Trauma
    - Others

Circumscribed Island of Bone in Deep Dermis

(Left) Low-power view shows a well-circumscribed island of bone within the deep dermis and subcutis. (Right) Higher power view demonstrates mature, well-formed bone with marrow spaces.



Mature Bone With Marrow Spaces

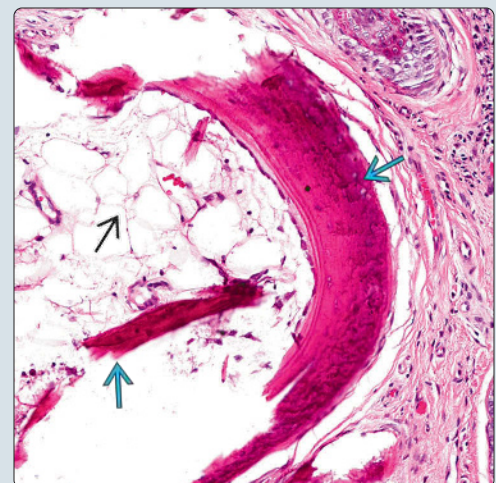


Large Dermal Nodules of Mature Bone With Marrow Spaces

(Left) This case demonstrates a more superficial dermal nodule composed of mature bone and a central cavity of marrow space. Note the numerous hair follicles indicative of this lesion being from the face. (Right) Higher power view demonstrates a well-circumscribed dermal nodule composed of mature bone with a central cavity.



Mature Bone With Central Cavity





## TERMINOLOGY

### Definitions

- Benign osseous tissue in dermis or subcutis
- Strictest definition is **primary** ossification of cutaneous tissue
  - As opposed to secondary calcification arising due to preceding inflammatory, neoplastic or traumatic insult

## CLINICAL ISSUES

### Presentation

- Single or multiple firm dermal papules, plaques, or subcutaneous nodules
- Cutaneous osteomas
  - May be single or multiple
  - Albright hereditary osteodystrophy should be investigated when presenting early in life
- Albright hereditary osteodystrophy
  - Autosomal dominant inheritance
  - Multiple osteomas plus
    - Pseudohypoparathyroidism
    - Brachydactyly
    - Obesity
    - Mental retardation
    - Short stature
    - Round facies
- Progressive osseous heteroplasia
  - Skin lesions develop within 1st months of life
  - Initially in dermis and progress into deeper tissue including muscle and tendons
- Plate-like osteoma cutis
  - Similar to progressive osseous heteroplasia, however, with more limited disease
- Miliary osteomas of face
  - Small ossified white or bluish papules on face of middle-aged adults
  - May or may not be due to prior acne vulgaris

### Treatment

- Surgical approaches
  - Surgical excision
- Drugs
  - Tretinoin
    - Used in cases of multiple miliary osteomas
- Laser resurfacing can also be used

### Prognosis

- Excellent
  - Lesions are benign

## MICROSCOPIC

### Histologic Features

- Mature lamellar bone within dermis or subcutis
- Marrow spaces may be present
- Osteoblasts may be present

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Osteochondroma

- Mature cartilage with layer of lamellar bone
- Extraskelatal/dermal osteosarcoma
  - Ill-defined with pleomorphic cells
  - Multinucleate giant cells
  - Hyperchromatic osteoblasts
- Secondary ossification due to
  - Preceding inflammation
    - Hair follicle in folliculitis
  - Neoplasm
    - Basal cell carcinoma
    - Pilomatricoma
    - Cysts (especially pilar cysts)
    - Melanocytic nevus (nevus of Nanta)
  - Trauma
  - Others
- Calcinosis cutis
  - Calcium deposition without mature bone formation

### Clinical

- Calcinosis cutis
  - Biopsy easily distinguishes
- Myositis ossificans
  - Typically more deep seated within muscle, soft tissue, or joints
  - Usually presents as tender, painful enlarging mass located in large muscles of extremities
- Pilomatrixoma
  - May show tent sign clinically
    - Stretching of skin gives lesion angulated appearance
  - Often occurs on head and neck of children
  - Biopsy easily distinguishes
- Gouty tophus
  - Usually involves single joint and often accompanied by excruciating pain
  - Usually accompanied by signs of inflammation
    - e.g., warmth, pain, redness, and swelling
  - Biopsy easily distinguishes

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Mature, benign-appearing ectopic bone within dermis or subcutis

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## KEY FACTS

## TERMINOLOGY

- Inadequate purine metabolism leading to elevated uric acid levels

## CLINICAL ISSUES

- Sex
  - Male predominance
- Age
  - Typically 30-50 years at presentation
- Ethnicity
  - More common in black patients
- Acute, exquisitely painful monoarticular arthritis
- Classically 1st metacarpophalangeal joint of great toe: Podagra
- Other lower extremity joints are commonly affected
- Chronic disease leads to crystal deposition in joints and eventual joint disability/immobility
- Long term affects may also include large collections of gout crystals: Gouty tophi

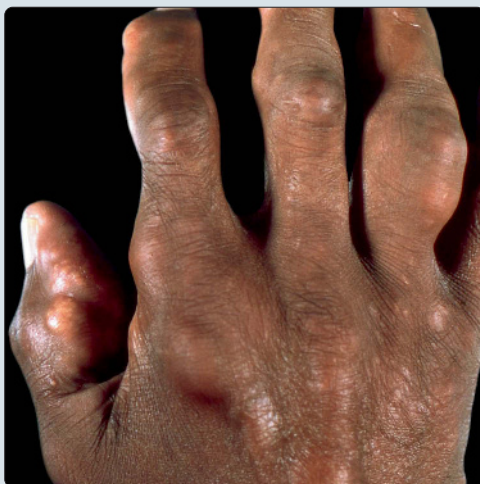
- Seen over digits, elbows, and on ears most frequently
- Chalky material if traumatized or otherwise opened
- Miliarial gout
  - Numerous grouped papules containing white or creamy material
  - May occur over joints as well as extensor surfaces of extremities as well as trunk

## MICROSCOPIC

- Important note
  - To demonstrate gout crystals, whether in tissue sections or on scrapings, specimen must be fixed in alcohol and processed without any water-soluble chemicals
  - Hydrous chemicals dissolve out crystals
- Amorphous pale pink or white material in dermis or subcutaneous tissue
- Granulomatous infiltrate surrounds amorphous material
- May have focal calcification

Affected Bony Prominences

**(Left)** Gout tophi typically appear over bony prominences such as finger joints as well as elbows. **(Right)** Well-circumscribed nodules of amorphous eosinophilic material are present within the dermis and subcutaneous tissue. Notice the overlying acanthosis and hyperkeratosis which indicate an acral location.

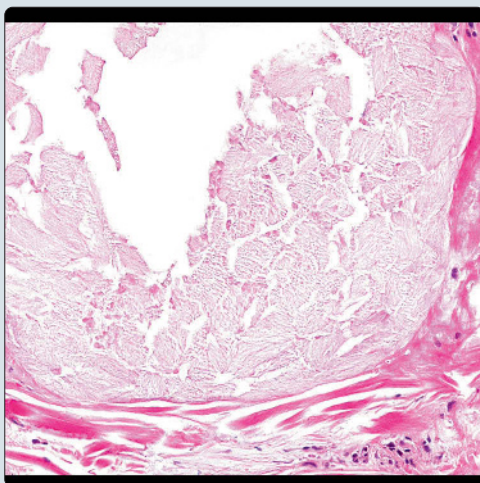


Nodules Within Skin

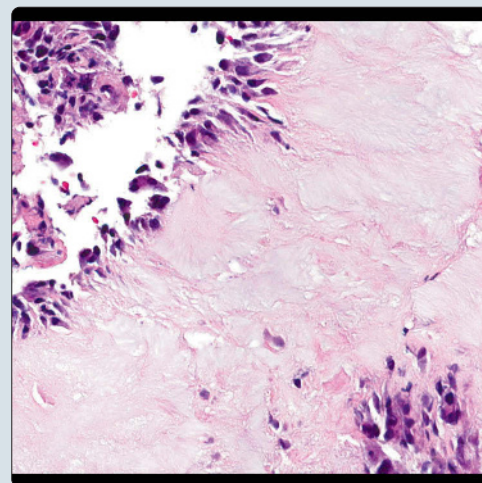


Amorphous Material

**(Left)** The area where the gout crystals were/are present (usually washed away during processing in aqueous solutions) is amorphous and weakly eosinophilic. Residual needle-shaped clefts are present where the crystals once were. **(Right)** Around the amorphous material, there are often histiocytes, and sometimes well-formed granulomas may be seen.



Surrounding Histiocytes



**TERMINOLOGY****Definitions**

- Inadequate purine metabolism leading to elevated uric acid levels

**ETIOLOGY/PATHOGENESIS****Various Mechanisms of Dysfunctional Purine Metabolism**

- Reduced excretion
  - Kidney disease, diuretic therapy
- Hyperuricemia
  - Starvation, sarcoidosis, psoriasis, diabetic ketoacidosis
- Increased purine synthesis
  - Myeloproliferative diseases after induction chemotherapy
- Genetic causes of purine metabolism
  - Glucose-6-phosphatase deficiency
  - Hypoxanthine guanine phosphoribosyltransferase mutations
  - Others

**CLINICAL ISSUES****Epidemiology**

- Sex
  - Male predominance
- Age
  - Typically 30-50 years at presentation
- Ethnicity
  - More common in black patients

**Presentation**

- Acute, exquisitely painful monoarticular arthritis
  - Erythematous, hot, swollen joint
  - Intense pain, especially with any physical contact
- Classically 1st metacarpophalangeal joint of great toe: Podagra
  - Other lower extremity joints are commonly affected
- Recurrent, especially when not on medication
- Chronic disease leads to crystal deposition in joints and eventual joint disability/immobility
- Long-term affects may also include large collections of gout crystals: Gouty tophi
  - Seen over digits, elbows, and on ears most frequently
  - Chalky material if traumatized or otherwise opened
- Miliarial gout
  - Numerous grouped papules containing white or creamy material
  - May occur over joints as well as extensor surfaces of extremities as well as trunk
- Contributing factors
  - Dietary factors: Alcohol intake, excessive food consumption (especially proteins)
  - Purine metabolism factors mentioned above

**Treatment**

- Drugs
  - Allopurinol, probenecid, febuxostat

**MICROSCOPIC****Histologic Features**

- Important note
  - To demonstrate gout crystals, whether in tissue sections or on scrapings, specimen must be fixed in alcohol and processed without any water-soluble chemicals
    - Hydrous chemicals dissolve out crystals
      - May be able to see empty spaces of crystals, but polarization microscopy will be negative
- Amorphous pale pink or white material in dermis or subcutaneous tissue
- Granulomatous infiltrate surrounds amorphous material
- May have focal calcification

**Cytologic Features**

- If scraping of chalky areas is performed, needle-shaped crystals can be seen
  - Negative birefringence with polarization microscopy

**DIFFERENTIAL DIAGNOSIS****Clinical**

- Cellulitis/septic joint
  - Infectious process can usually be found via culture
  - Joint aspiration yields marked neutrophil infiltrate
  - Skin biopsy in cellulitis shows diffuse neutrophil infiltrate
  - No crystal deposition
- Autoimmune arthritis
  - Usually bilateral and involve multiple joints
  - Anti-RF &/or ANA antibodies can typically be identified
  - Not an acute arthritis
- Psoriatic arthritis
  - Clinical history of concurrent psoriasis
  - Not typically an acute arthritis, but flares can be acutely painful
  - Joint damage can be demonstrated via x-ray in many cases

**Histopathological**

- Colloid milium
  - Amorphous eosinophilic material in superficial dermis
  - No crystal deposition
  - Nonspecific lymphocytic infiltrate, but granulomatous inflammation is not typical
- Nodular amyloidosis
  - Amorphous eosinophilic material in superficial dermis
  - No crystal deposition
  - A granulomatous inflammation is not typical
    - Plasma cells may be seen
    - In some cases, amyloid is deposited around blood vessels

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## Tattoo Ink

## KEY FACTS

**TERMINOLOGY**

- Tattoo reactions include tattoo granuloma, amalgam tattoo, and carbon tattoo

**ETIOLOGY/PATHOGENESIS**

- All tattoos, whether accidental, iatrogenic, or decorative, are due to introduction of exogenous pigments into skin
- Tattoo reactions may be immunologic, infectious, or neoplastic

**CLINICAL ISSUES**

- Eczematous, lichenoid, or dermal papules, plaques, or nodules localized to site of tattoo

**MICROSCOPIC**

- Spongiotic, lichenoid, granulomatous, pseudolymphomatous, or mixed tissue reaction pattern

**ANCILLARY TESTS**

- Fontana-Masson is negative in tattoo pigments

- Clonality studies may be helpful in excluding lymphoid neoplasms in cases of pseudolymphomatous reactions

**TOP DIFFERENTIAL DIAGNOSES**

- Melanocytic neoplasms
  - Can be readily distinguished from tattoo by morphology; stains for melanin, such as Fontana-Masson; or immunoperoxidase for melanocytic markers
- Sarcoidosis
  - Distinction often requires clinical evaluation as true sarcoidosis occurring at site of tattoo (Koebner phenomenon) can be indistinguishable histopathologically

**DIAGNOSTIC CHECKLIST**

- Granulomatous tattoo reactions may be histologically indistinguishable from sarcoidosis due to koebnerization

**Contact Dermatitis Restricted to Tattooed Skin**

*Allergic contact dermatitis due to paraphenylenediamine in henna tattoo shows restriction of lesions to tattooed skin. (Courtesy E. Velazquez, MD.)*



## TERMINOLOGY

### Synonyms

- Tattoo granuloma
- Amalgam tattoo
- Carbon tattoo
- Tattoo reaction

### Definitions

- Deposition of exogenous pigment into skin

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- Tattoos may be accidental (carbon tattoo), iatrogenic (Monsel solution, ferrous subsulfate for hemostasis), or decorative
- All tattoos, whether or not associated with immunologic reactions, transmissible infections, or neoplasms, are due to introduction of exogenous pigments into skin
- Red pigments, such as mercuric sulfide or cadmium selenide, are most commonly associated with immunologic reactions
- Carbon and amalgam are associated with black discoloration, while ferric oxide and ferrous subsulfate are associated with brown pigmentation
- Manganese, cobalt, chromic oxide, cadmium sulfide, and titanium oxide are used in purple, blue, green, yellow, and white pigments, respectively
- Amalgam tattoo is most common exogenous oral pigmentation and is most often found on gingival mucosa
  - It is widely used restorative element used in tooth filling and contains metal components, such as silver, mercury, and tin

## CLINICAL ISSUES

### Presentation

- Clinical presentation varies depending on type of reaction
- In absence of reaction, decorative or accidental pigmentation is identified
- Carbon, amalgam, and pigments associated with brown discoloration may be mistaken for melanocytic nevi or melanoma
- Numerous types of reactions have been described
  - Allergic contact dermatitis presents with vesicular or scaly papules and plaques
  - Phototoxic reactions present with sunburn-like findings
  - Granulomatous reactions result in dermal papules, plaques, or nodules, while lichenoid reactions are associated with lichen planus-like lesions
  - Pseudolymphomatous reactions to tattoo are described as erythematous or violaceous nodules
  - Reactions are usually confined to tattoo site but may become systematized
    - With exception of phototoxic reactions, which are associated with yellow tattoos, all of these reactions are most frequently due to red pigments
- Transmission of infections, such as tuberculosis, HIV, hepatitis, and Hansen disease, have been reported

- Atypical mycobacteria, such as *Mycobacterium fortuitum* and *Mycobacterium chelonae*, have caused infections in tattoo sites sporadically and as outbreaks due to contamination of premixed ink
- Associated neoplasms include verrucae vulgares, verrucae plana, and eruptive keratoacanthomas
  - While warts are more often associated with black ink, keratoacanthomas and pseudocarcinomatous hyperplasia are more often associated with red ink

### Treatment

- Surgical approaches
  - Laser tattoo removal uses selective photothermolysis to target and destroy pigment in dermis and is effective in patients  $\pm$  tattoo reactions
    - For example, lichenoid and spongiotic tattoo reactions to red ink have resolved following treatment with Q-switched 532 nm Nd:YAG laser
  - Q-switched ruby and alexandrite lasers have been used for cosmesis of amalgam tattoos
  - Surgical excision is reserved for refractory cases
- Drugs
  - Topical, intralesional, and systemic steroids have been used successfully, but reactions often recur upon treatment discontinuation
  - Allopurinol treatment has been reported for case of tattoo granuloma

### Prognosis

- Tattoo reactions are often chronic, persistent, and may recur following treatments
- Spontaneous resolution has been reported

## MICROSCOPIC

### Histologic Features

- In amalgam tattoo, black granular deposits are seen on elastic or collagen fibers of submucosa; however
  - Unlike cutaneous tattoos, granulomatous reactions are uncommon
  - Mast cell infiltration is common
  - Lichenoid reactions simulating oral lichen planus have been frequently reported
- Carbon tattoo is similar: Aggregates of granular black pigment usually without inflammation
- Ferrugination due to Monsel solution demonstrates large polygonal, multinucleated, and sometimes atypical histiocytes with clumps of dark brown fine pigment
- Allergic contact dermatitis demonstrates acute or subacute spongiosis, often with eosinophils
  - In contrast, phototoxic reactions show vacuolar change, exocytosis of neutrophils, edema and vasodilation, and keratinocyte necrosis ("sunburn cells") limited to upper layers of epidermis
- Granulomatous reactions to tattoo ink may be sarcoidal (foreign body granuloma), palisading, and rarely tuberculoid (caseating)
  - Palisading granulomas may feature necrobiosis and mimic granuloma annulare, including perforating variant or necrobiosis lipoidica
- Lichenoid tattoo reactions feature band-like lymphocytic infiltrate with vacuolar change, necrotic keratinocytes, and pigment incontinence

- Reactions analogous to pseudolymphoma [cutaneous lymphoid hyperplasia (CLH)] demonstrate well-formed germinal centers and mixed infiltrates, often with eosinophils
  - These reactions may be coupled with interface dermatitis; T-cell variant of CLH is predominant subtype
  - Polyclonality, identification of tattoo pigment, and focal granulomas allow distinction from lymphoid neoplasm

## ANCILLARY TESTS

### Histochemistry

- Melanin stains (Fontana-Masson) are negative in tattoo pigments
- Iron stain (Perl) is negative in most tattoos but is positive in ferrugination due to Monsel solution

### Immunohistochemistry

- Immunohistochemistry has demonstrated that infiltrate in lichenoid reactions is cytotoxic, with predominance of CD8 and CD56 (+) cells

### Clonality Studies

- In situ hybridization for light chain restriction or T- or B-cell gene rearrangement may sometimes be helpful in excluding lymphoid neoplasms in cases of pseudolymphomatous reactions

## DIFFERENTIAL DIAGNOSIS

### Melanocytic Neoplasms

- Tattoo with pigmentation due to brown or black pigments may be mistaken for tumoral melanosis or heavily pigmented melanocytic neoplasms, such as cellular blue nevus or melanoma
- Rarely, tattoo pigment may migrate to lymph nodes, and cases of pigmented lymphadenopathy secondary to black tattoo pigment have been reported in literature
  - Pigment-laden macrophages with granular black material are seen in lymph nodes
- However, these entities can be readily distinguished from tattoo by morphology; stains for melanin, such as Fontana-Masson; or immunoperoxidase for melanocytic markers

### Sarcoidosis

- Sarcoidal granulomatous tattoo reactions may be 1st and sometimes only cutaneous manifestation of systemic sarcoidosis, and patients may be asymptomatic
- Additionally, histology of sarcoidal foreign body granuloma due to tattoo and true sarcoidosis occurring at site of tattoo (Koebner phenomenon) are often indistinguishable
  - Therefore, distinction often requires clinical evaluation

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Tattoo reactions may be spongiotic, lichenoid, granulomatous, or pseudolymphomatous
- Neoplasms including warts and keratoacanthomas or infections may arise in tattoos

## Pathologic Interpretation Pearls

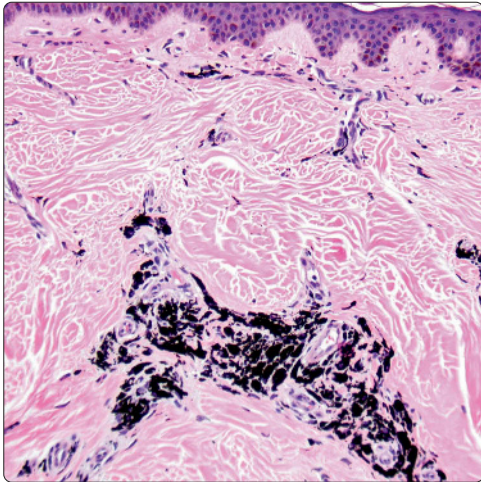
- Sarcoidal granulomatous tattoo reactions are histologically indistinguishable from true sarcoidosis due to koebnerization

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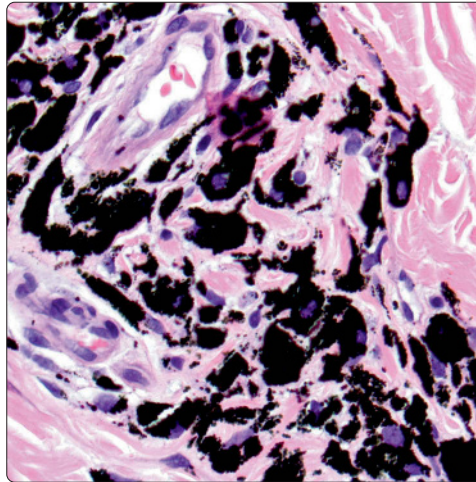
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**Black Granular Pigment**

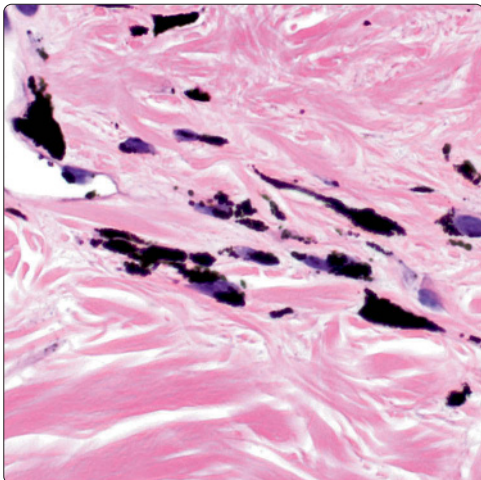


**Jet Black Granular Pigment**

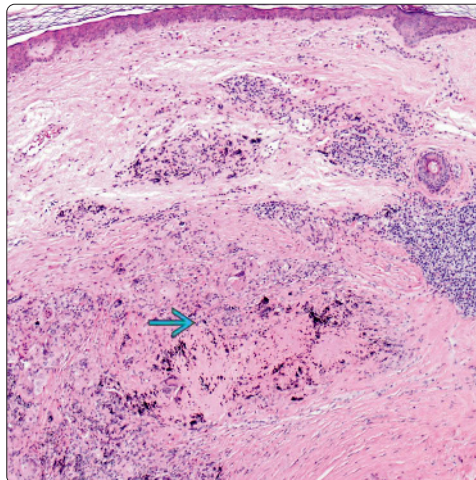



(Left) Carbon tattoo shows black granular pigment within the dermis. The clinical diagnosis was blue nevus. (Right) High-power view of a carbon tattoo demonstrates jet black granular material within the cytoplasm of histiocytes as well as free within the dermis without significant surrounding inflammation.

**Intracellular and Extracellular Pigment Deposition**

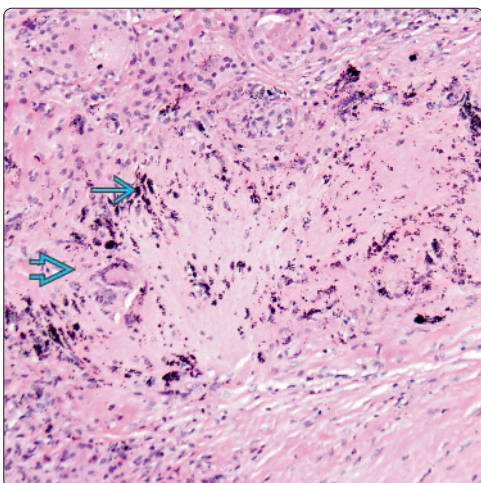


**Granulomatous Reaction to Exogenous Pigment**

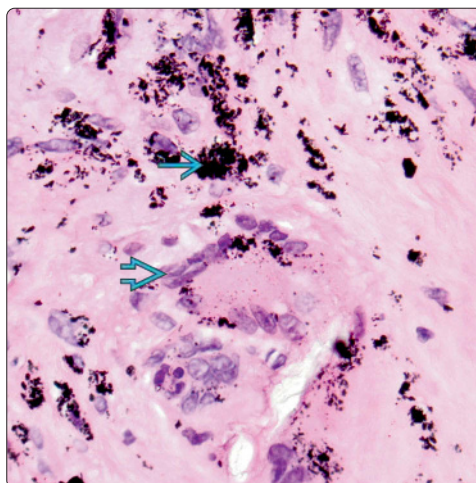






(Left) Intracellular and extracellular black granular pigment is evident in this example of a carbon tattoo. (Right) Granulomatous tattoo reaction shows a granulomatous  dermatitis with exogenous pigment.

**Granulomatous Reaction With Multinucleated Giant Cells**



**Multinucleated Giant Cell With Pigment**



(Left) Granulomatous tattoo reaction shows granulomas  with abundant exogenous pigment . (Right) Multinucleated giant cells  and tattoo pigment  are shown here in a biopsy of a granulomatous reaction to tattoo ink.



## KEY FACTS

### TERMINOLOGY

- Synthetic materials injected into dermis to add volume to face and other areas for cosmetic enhancement

### CLINICAL ISSUES

- Patients present with nodules, plaques, and discoloration overlying areas where fillers were injected
- Most reactions present months after injection
- Tenderness or purulence could signal infection
- Severe filler reactions occur acutely and lead to tissue necrosis or blindness
- More commonly, patients present months later with papules and nodules secondary to granuloma or accumulated filler material

### MICROSCOPIC

- Each filler material has recognizable histological appearance

- Hyaluronic acid: Mucinous appearance (blue amorphous material, granular)
- Poly-L-lactic acid: Polarizable polygonal or spiky crystals
- Calcium hydroxylapatite: Blue-gray spheres
- Polymethyl methacrylate: Translucent uniform spheres
- Silicone: Swiss cheese appearance with variably sized translucent spheres, fibrosis, and granuloma

### TOP DIFFERENTIAL DIAGNOSES

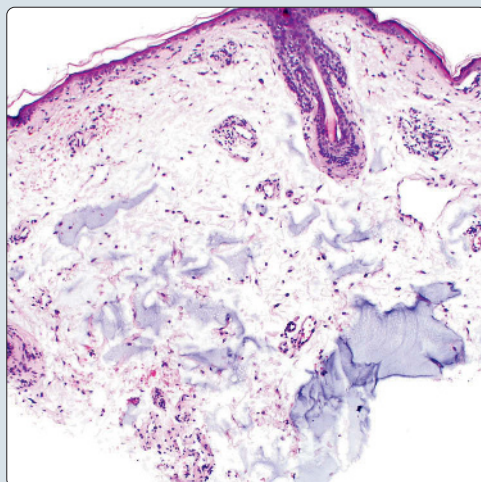
- Mycobacterial infection
- Cellulitis

### DIAGNOSTIC CHECKLIST

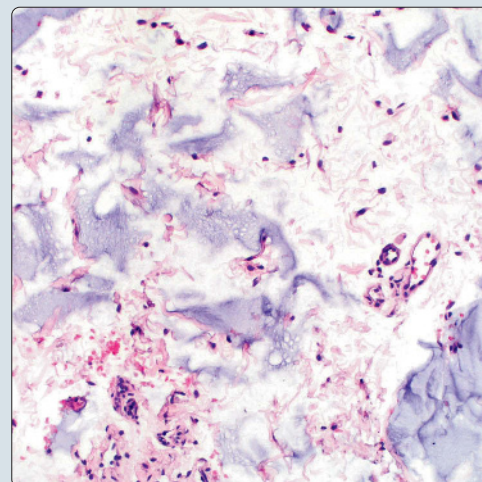
- Most common reaction pattern is foreign body granuloma leading to delayed presentation of subcutaneous nodules at injection site
- Each filler material has unique histological appearance

**Hyaluronic Acid Filler**

*(Left) Hyaluronic acid fillers appear as acellular blue aggregates in the dermis. (Right) Hyaluronic acid filler material in the dermis resembles endogenous mucin, appearing to form aggregates of blue granular or bubbly material.*

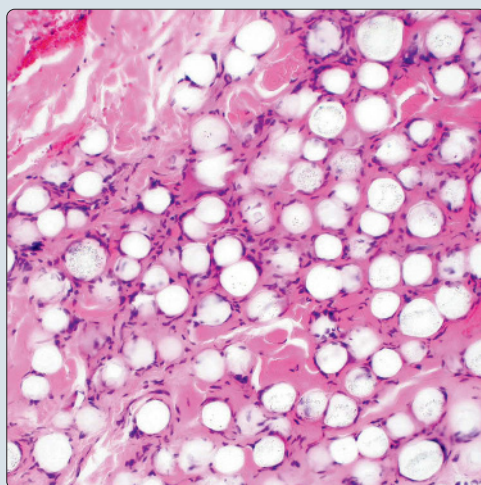


**Hyaluronic Acid Material in Dermis**

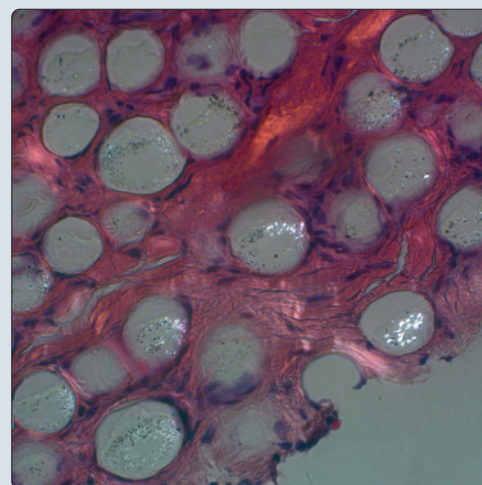


**Polymethyl Methacrylate**

*(Left) Polymethyl methacrylate filler material is recognizable as relatively uniform translucent or slightly granular spheres in the dermis, surrounded by fibrosis and granulomatous inflammation. (Right) Polymethyl methacrylate filler material is recognizable as spheres with refractility on polarizing microscopy.*



**Polarizing Microscopy of Polymethyl Methacrylate**



## TERMINOLOGY

### Synonyms

- Soft tissue fillers
- Dermal fillers

### Definitions

- Synthetic materials injected into dermis to add volume to face and other areas for cosmetic enhancement

## ETIOLOGY/PATHOGENESIS

### Complications From Filler Injections

- Vascular occlusion or compression leads to necrosis
- Embolism of material within retinal artery may lead to blindness
- Introduction of infectious organisms or biofilm leads to cellulitis or other chronic infection
- Agglutination of filler material leads to nodules
- Foreign body reaction leads to granulomas

### Commonly Used Fillers

- Hyaluronic acid (HA)
- Poly-L-lactic acid (PLLA)
- Calcium hydroxylapatite
- Polymethylmethacrylate (PMMA)
- Silicone

## CLINICAL ISSUES

### Epidemiology

- Serious complications from fillers (necrosis, blindness) are extremely rare events and occur immediately or within days after injection
- More common adverse events include nodules and foreign body reactions which occur in delayed fashion (months after injection)

### Presentation

- Patients present with nodules, plaques, and discoloration overlying areas where fillers were injected
- Most reactions present months after injection
- Tenderness or purulence could signal infection

### Treatment

- Surgical approaches
  - Superficially situated nodules can be incised and evacuated
- Drugs
  - Foreign body reactions can be treated by injecting intralesional corticosteroid
  - Hyaluronidase can be injected into nodules formed by accumulations of HA fillers
  - Antibiotic treatment is necessary for any infectious complications

### Prognosis

- Most complications can be managed through procedural correction and medical treatment

## IMAGING

### Radiographic Findings

- Calcium hydroxylapatite is radiopaque

## MICROSCOPIC

### Histologic Features

- Most common reaction to fillers is granulomatous (foreign body) reaction characterized by multinucleate giant cells, dermal fibrosis, and identifiable foreign material
- HA: Amorphous blue material with somewhat granular appearance, uncommonly induces granuloma formation
- PLLA: Polarizable translucent polygonal or spiky crystals surrounded by histiocytes and within multinucleate giant cells
- PMMA: Circumscribed round translucent spheres within histiocytes
- Calcium hydroxylapatite: Blue-gray spheres with granulomatous inflammation
  - Calcium can be identified by von Kossa stain
- Silicone: Swiss cheese appearance with fibrosis, granulomatous inflammation, and variably sized spherical empty spaces

## ANCILLARY TESTS

### Histochemistry

- Special stains (Fite, Gram) should be used if infection is suspected

### Infections

- Tissue culture may be necessary if infection is suspected

## DIFFERENTIAL DIAGNOSIS

### Mycobacterial Infection

- Foamy macrophages predominate (histiocytic variant of leprosy)
  - Multinucleated giant cells are typically not seen
- Does not have polarizable or identifiable foreign material identifiable within multinucleated giant cells
- Fite stain &/or culture may be necessary to rule out

### Cellulitis

- Biopsy should easily decipher
  - No obvious foreign or polarizable material identified

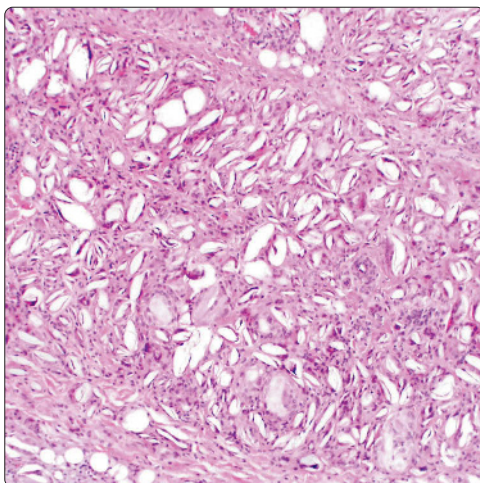
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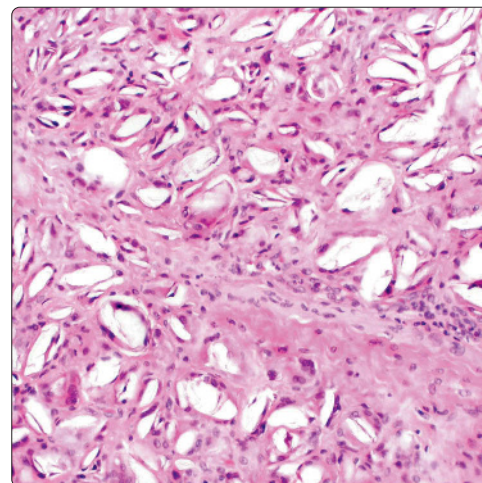


**(Left)** Poly-L-lactic acid fillers are polygonal crystalline forms in the dermis surrounded by granulomatous inflammation. **(Right)** Poly-L-lactic acid filler material appears as polymorphous polygonal and crystalline forms.

Poly-L-Lactic Acid

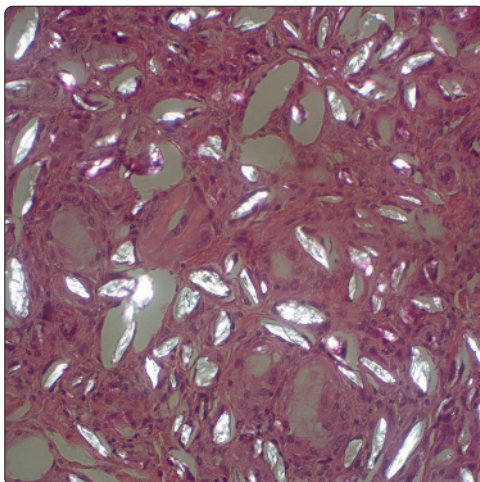


Poly-L-Lactic Acid Filler Material

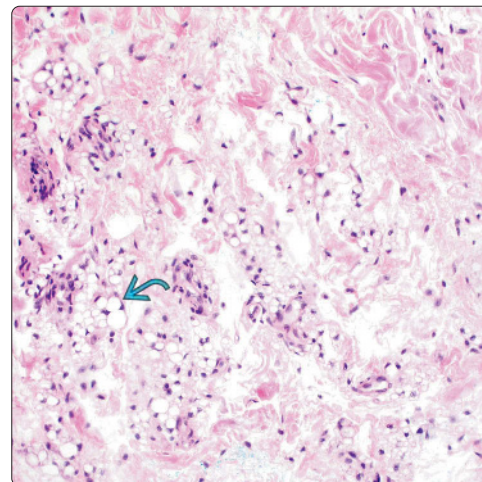


**(Left)** Polarizing microscopy of poly-L-lactic acid reveals refringence of filler material. **(Right)** A low-power view of silicone filler granuloma demonstrates variably sized, spherical empty spaces that can impart a Swiss cheese appearance.

Polarizing Microscopy of Poly-L-Lactic Acid

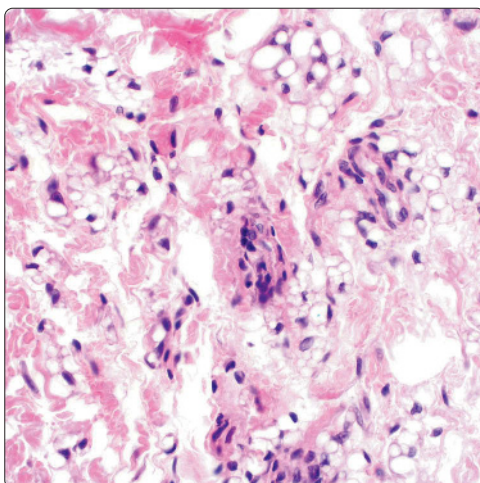


Low-Power View of Silicone Filler

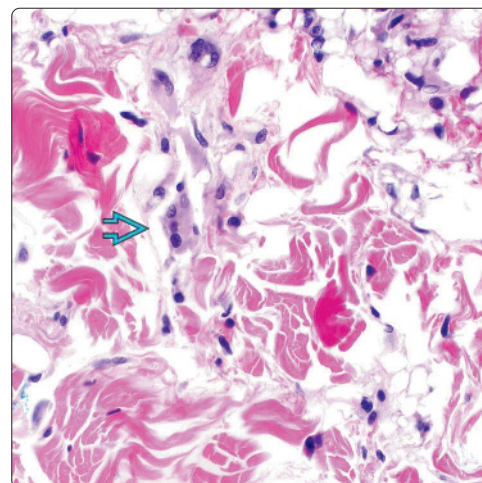


**(Left)** Silicone filler material forms a Swiss cheese appearance in the dermis, with vacuolated histiocytes and granulomatous inflammation. **(Right)** Intracytoplasmic vacuoles within histiocytes characterize silicone granuloma. A multinucleate histiocyte is seen.

Silicone Granuloma

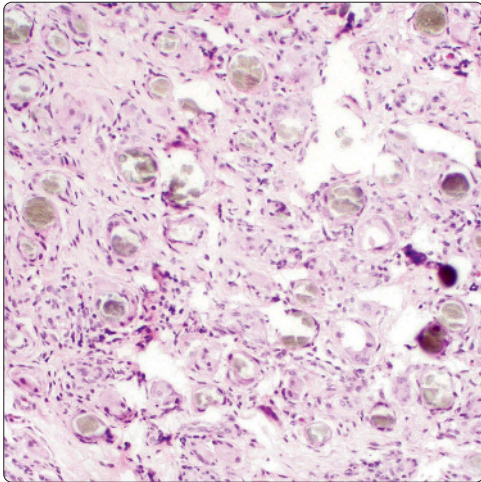


Granulomatous Dermatitis Secondary to Silicone Filler Material

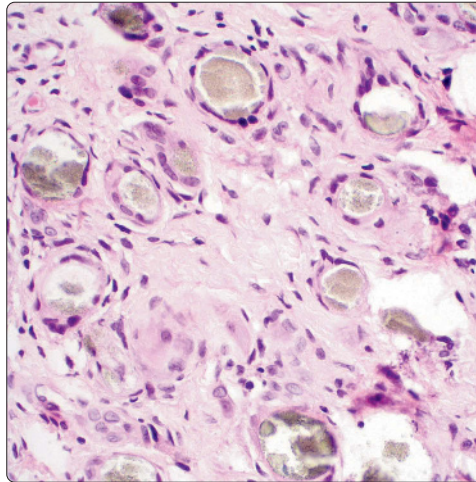




**Low-Power View of Calcium Hydroxylapatite**

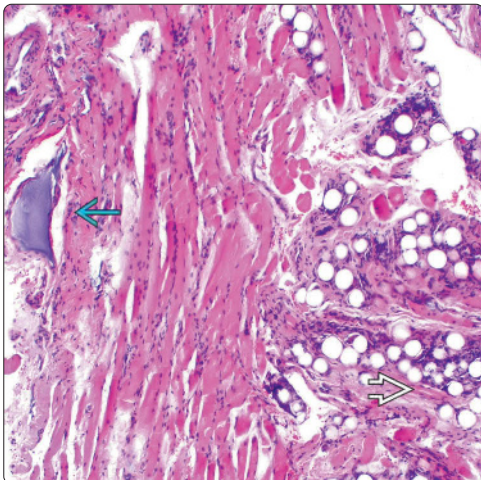


**Calcium Hydroxylapatite**

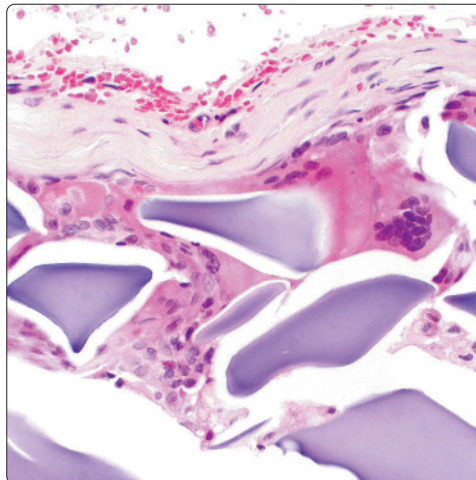


**(Left)** A low-power view of calcium hydroxylapatite demonstrates blue-gray spheres with surrounding granulomatous inflammation with some multinucleated histiocytes. **(Right)** Calcium hydroxylapatite filler material is recognizable as green to gray fissured spheres in the dermis, surrounded by granulomatous inflammation.

**Multiple Filler Materials**

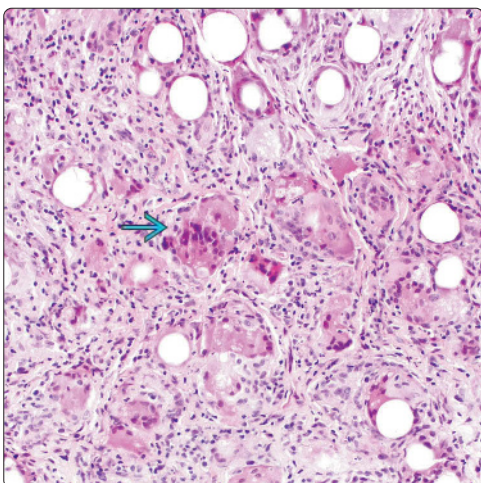


**Granulomatous Inflammation With Multinucleated Giant Cells**

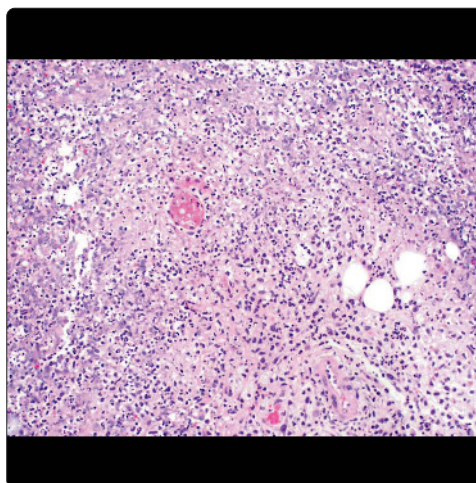


**(Left)** It is not uncommon for patients to have more than 1 type of filler material injected during cosmetic procedures. In this example, hyaluronic acid particles (blue) are seen in addition to polymethyl methacrylate beads (black). **(Right)** Multinucleate giants engulf foreign material as part of the foreign body reaction. In this case, nodular accumulations of hyaluronic acid are seen within the cytoplasm of multinucleate giants cells.

**Granulomatous Dermatitis**



**Suppurative Inflammation**



**(Left)** Any of the filler materials are capable of inducing a foreign body reaction, characterized by granulomatous inflammation with multinucleated histiocytes (blue) and stromal fibrosis. **(Right)** The presence of suppurative inflammation or neutrophil-rich infiltrates in the dermis should raise the possibility of an infectious complication of filler injection rather than foreign body reaction.



# Silicone Reaction

## KEY FACTS

### TERMINOLOGY

- Can be due to silicone from ruptured breast implants or injectable permanent aesthetic microimplants

### CLINICAL ISSUES

- Breast implants
  - Nodules may form in skin &/or soft tissue around implants
  - May also have nodules along lymphatic spread
    - Including axillary nodules
  - Newer silicone gel implants can transform to liquid silicone at body temperature enabling local and distant spread
  - Nodule formation may take months or years
    - Release of silicone into surrounding soft tissue relies on degradation of outer shell
  - Rupture may cause formation of breast capsules around implant
- Injectable cosmetic fillers

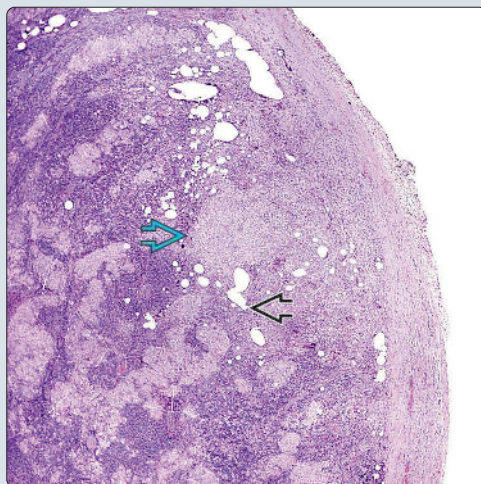
- Initially after injection
  - May have erythema, edema, and bruising
- Weeks or months after injection
  - Nodules usually arise in areas where silicone filler is injected

### MICROSCOPIC

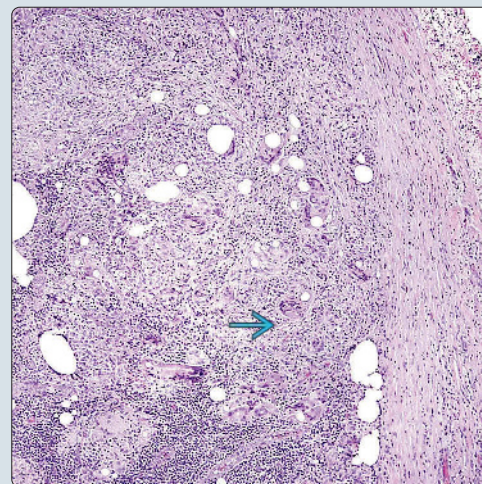
- Silicone nodules contain numerous empty-appearing spaces
  - May occasionally contain clear silicone in these spaces
    - Usually washed away during tissue processing
- Varying sizes and shapes
  - Swiss cheese appearance
- Vacuoles may be present in dermis, subcutaneous tissue, or deeper soft tissues depending on source
- Granulomatous infiltrate with numerous multinucleated giant cells containing intracytoplasmic vacuoles
- Fibrosis/scarring may be feature depending on age of silicone nodule

**Silicone in Lymph Node**

**(Left)** Although this is a picture of a lymph node involved by silicone migration, the changes are virtually identical to the skin. There are numerous granulomas with variably sized clear spaces. **(Right)** At higher power, the variation in size of the clear spaces is better appreciated. Multinucleated giant cells can also be found throughout the granulomatous inflammation, and many of them are wrapping around the clear spaces.

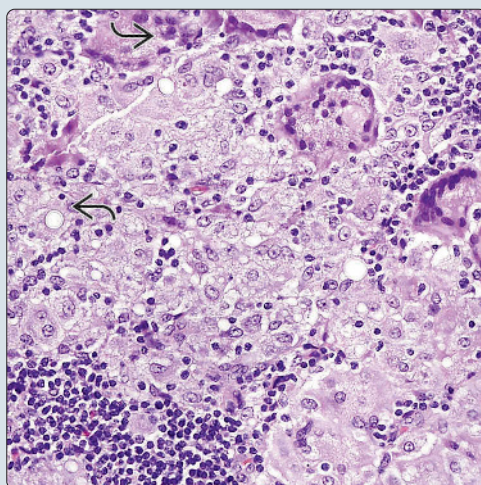


**Variably Sized Clear Spaces**

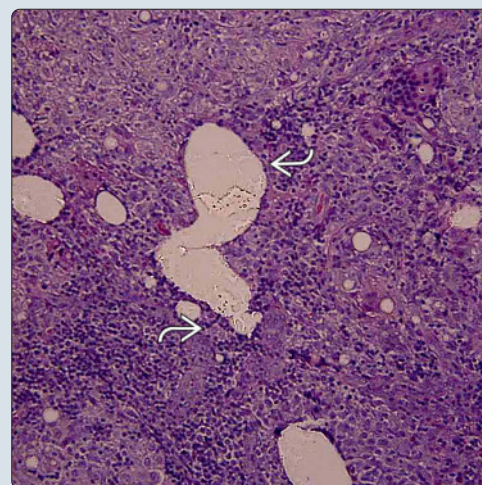


**Multinucleated Giant Cells**

**(Left)** Even at higher power, small clear spaces can be found within the cytoplasm of background histiocytes. **(Right)** If you turn the condenser down on the microscope, residual silicone can sometimes be found within the clear spaces.



**Silicone in Clear Spaces**



## TERMINOLOGY

### Definitions

- Can be due to silicone from ruptured breast implants or injectable permanent aesthetic microimplants

## CLINICAL ISSUES

### Presentation

- Breast implants
    - Nodules may form in skin &/or soft tissue around implants
      - May also have nodules along lymphatic spread
        - Including axillary nodules
    - Newer silicone gel implants can transform to liquid silicone at body temperature enabling local and distant spread
  - Nodule formation may take months or years
    - Release of silicone into surrounding soft tissue relies on degradation of outer shell
  - Some silicone breast implants may break in first 3 years
    - Not uncommon for women to have modern implants for 10 years or more
    - Rate of rupture begins to increase significantly after 10 years, with rupture (silent or symptomatic) of 1 implant usually during years 11-20
  - Rupture may cause formation of breast capsules around implant
  - Rupture may also lead to ipsilateral axillary lymphadenopathy due to silicone migration
- Injectable cosmetic fillers
  - Silicone-based fillers are less commonly used in routine cosmetic dermatology
  - Initially after injection
    - May have erythema, edema, and bruising
  - Weeks or months after injection
    - Nodules usually arise in areas where silicone filler is injected
      - May also have spread of silicone beyond local area with subsequent nodule formation

### Treatment

- Surgical approaches
  - Removal of silicone and its corresponding granulomatous infiltrate usually takes surgical excision
- Dermabrasion
  - Recent study showed efficacy of dermabrasion at resolving silicone granulomas

## MICROSCOPIC

### Histologic Features

- Silicone nodules contain numerous empty-appearing spaces
  - May occasionally contain clear silicone in these spaces
    - Usually washed away during tissue processing
    - Silicone itself is not polarizable, but impurities in silicone may polarize
- Varying sizes and shapes
  - Swiss cheese appearance
- Vacuoles may be present in dermis, subcutaneous tissue, or deeper soft tissues depending on source

- Granulomatous infiltrate with numerous multinucleated giant cells containing intracytoplasmic vacuoles
  - May be accompanied by lymphocytic infiltrate
    - Neutrophils present if there is concomitant infection
  - Fibrosis/scarring may be feature depending on age of silicone nodule
- Breast implant capsules are layers of fibrosis/sclerosis and often contain empty vacuoles, which contained silicone prior to processing
    - Also tend to have calcifications and granulomatous inflammation

## DIFFERENTIAL DIAGNOSIS

### Histopathological

- Foreign body granuloma
  - Often polarizable foreign material
  - May have nonpolarizable foreign material that is not removed during processing
- Tattoo granuloma
  - Nodule forms within tattoo
  - Tattoo pigment should be visible in and around granulomatous inflammation
- Granulomas due to other fillers
  - Collagen filler
    - Filler material is more eosinophilic, amorphous, and acellular
  - Polymethyl methacrylate microsphere (Artecoll)
    - Microspheres leave clear voids in tissue and multinucleated giant cells, which are all same size
  - Polyacrylamide gel (Aquamid)
    - Basophilic, amorphous material with areas of necrosis
  - Hyaluronic acid filler
    - Basophilic, amorphous material without necrosis
    - Alcian blue positive
  - Poly-L-lactic acid (Newfill, Sculptra)
    - Long, spiky, translucent figures in multinucleated giant cells
  - Polyalkylimide gel (bio-Alcamid)
    - Palisading granulomas with central degenerating material
      - Mimicker of other granulomatous diseases

### Clinical

- Abscess
  - Only in differential if nodule forms shortly after procedure with residual erythema and edema
- With clinical history of silicone near site of nodule formation, clinical differential is very narrow

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# Amalgam Tattoo

## KEY FACTS

### TERMINOLOGY

- Localized area of blue, gray, or black pigmentation caused by amalgam embedded into oral tissues, usually during dental procedures

### ETIOLOGY/PATHOGENESIS

- Commonly used dental amalgam, which contains silver, tin, mercury, and other materials, can be embedded into tissue during dental procedures

### CLINICAL ISSUES

- Presentation**
  - Blue-gray to black pigment most common on gingiva and buccal mucosa
  - Asymptomatic flat macule ranging from a few mm to > 1 cm
- Treatment**
  - Biopsy indicated if clinical diagnosis is uncertain
  - Can be removed for cosmesis

### IMAGING

- Generally not visible radiographically

### MICROSCOPIC

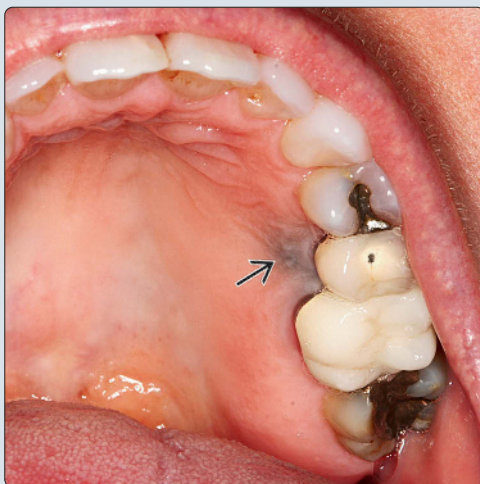
- Fine black granules within superficial connective tissue
- Pigment can be seen in collagen, histocytes, fibroblasts, elastic fibers, and around blood vessel walls
- Usually no inflammation associated with pigment
- Up to 38% of cases have foreign giant cell reaction

### TOP DIFFERENTIAL DIAGNOSES

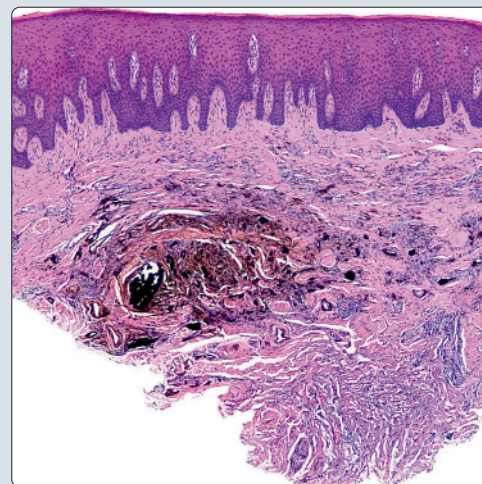
- Pigmented intraoral lesions**
  - Oral melanotic macule
  - Intraoral melanocytic nevus
  - Oral melanoma
- Varicosities**
- Unintentional mucosal tattoos**
  - Accidental placement of foreign material, such as pencil graphite

**Diffuse Blue-Gray Pigment in Oral Cavity**

(Left) Clinical photo shows diffuse blue-gray pigmentation typical for an amalgam tattoo. The tattoo could be related to the crowns on the premolar and molar teeth, or the amalgam restoration on the premolar tooth. (Right) H&E shows amalgam tattoo of the buccal vestibule with scattered large fragments of black material distributed in the lamina propria. The overlying epithelium is normal. Inflammation is noted, although many amalgam tattoos show little or no inflammation.

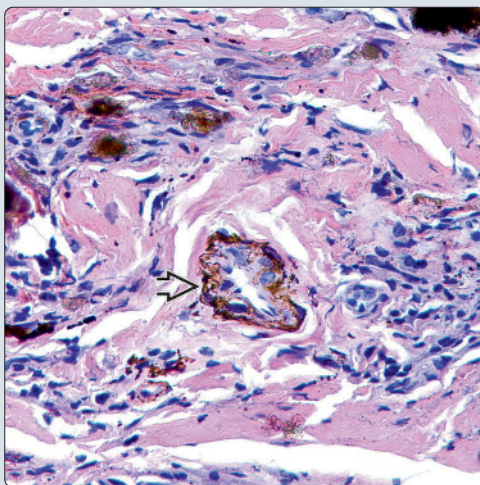


**Dark Solid Clumps of Amalgam**

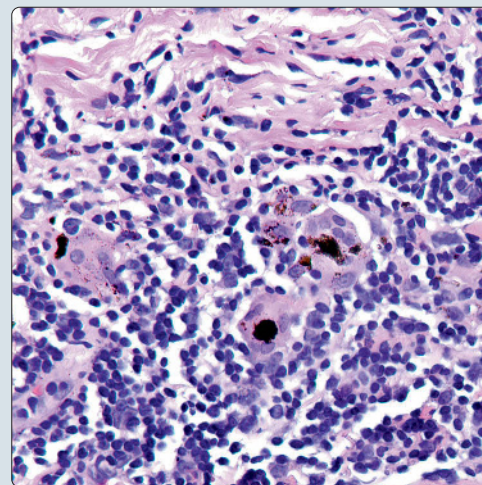


**Amalgam Tattoo Encircling Vessel**

(Left) High-power photomicrograph of an amalgam tattoo illustrates the perivascular location of the amalgam. The silver salts found in dental amalgam stain the reticulin fibers surrounding nerves and vessels. (Right) H&E shows amalgam tattoo eliciting a foreign body giant cell reaction. Amalgam pigment is seen within the scattered giant cells with associated plasma cells and lymphocytes. Radiographs can at times confirm the metallic nature of the tattoo.



**Foreign Body Giant Cell Reaction**



## TERMINOLOGY

### Definitions

- Localized area of blue, gray, or black pigmentation caused by amalgam embedded into oral tissues, usually during dental procedures
  - Amalgam is commonly used dental material containing silver, tin, mercury, and other materials

## ETIOLOGY/PATHOGENESIS

### Trauma

- Dental amalgam embedded into tissue during dental procedures

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Common
- Sex
  - No gender predilection

### Site

- Most commonly located on gingiva and buccal mucosa

### Presentation

- Asymptomatic flat macule ranging from few mm to > 1 cm
- Blue-gray to black pigmentation

### Treatment

- Biopsy indicated if clinical diagnosis is uncertain or for cosmetic reasons

## IMAGING

### Radiographic Findings

- Generally not visible radiographically

## MACROSCOPIC

### Size

- Ranging from few mm to > 1 cm

## MICROSCOPIC

### Histologic Features

- Fine, black granules scattered within superficial connective tissue
- Pigment can be seen in collagen, histocytes, fibroblasts, elastic fibers, and around blood vessel walls
- Usually no inflammation associated with pigment
- Foreign body multinucleated giant cell reaction reported in up to 38% of cases

## DIFFERENTIAL DIAGNOSIS

### Pigmented Intraoral Lesions

- Oral melanotic macule
  - Clinically appears brown rather than slate-gray
  - Microscopically, melanin pigment noted in basal cells and melanophages, and incontinent pigment is present in superficial connective tissue
- Intraoral melanocytic nevus

- Color ranges from light brown to dark brown to almost blue-black
- Intraoral nevus has histologic features of cutaneous counterpart: Junctional, compound, intramucosal (lamina propria), and blue
- Oral melanoma
  - Hard palate and maxillary alveolus are overwhelming sites for oral melanoma
  - Lesions are poorly defined and range in color from light brown to almost black
  - Satellite nests are often identified clinically

### Varicosities

- Thrombosed varix
  - Unlike amalgam tattoo, varix presents as soft tissue swelling

### Unintentional Mucosal Tattoos

- Accidental placement of foreign material, such as pencil graphite

### Intentional Mucosal Tattoos

- Cultural tattoos from some African countries most often seen on anterior facial gingiva
  - Gingiva has dense blue-black discoloration
- Tattoos placed on lower labial mucosa
  - Amateur tattoos generally with "slang" phrases

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Blue-gray to black flat macule in area on dental amalgam

### Pathologic Interpretation Pearls

- Black foreign pigment with little inflammation or melanocytic activity

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## KEY FACTS

**ETIOLOGY/PATHOGENESIS**

- Blue to gray pigmentation of skin due to prolonged exposure to silver directly through skin or via ingestion

**CLINICAL ISSUES**

- Occurs most commonly on sun-exposed areas of skin, although nail and mucosa can also be affected
- Argyria is not dangerous, but patient may experience systemic effects of silver toxicity

**MICROSCOPIC**

- Minute brown-black granules in dermis favoring sweat glands (especially in linear fashion outlining basement membrane zone of eccrine glands)
- Granules may also be found concentrated in perifollicular sheath, nerve, capillary walls, and elastic fibers

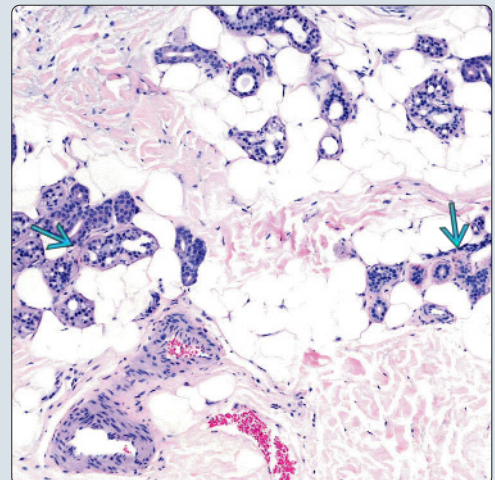
- Clumps of fine, pigmented particulate concentrated around blood vessels in superficial to middermis
- Pigment may be intracellular within macrophages or extracellular
- Blue nevus
  - Several variants exist
  - Most commonly shows dendritic melanocytes in sclerotic stroma with heavy pigmentation
  - Epidermis is spared
  - Dark granules are absent
- Drug hyperpigmentation
  - Minocycline
  - Amiodarone
  - Antimalarials
  - Others

**TOP DIFFERENTIAL DIAGNOSES**

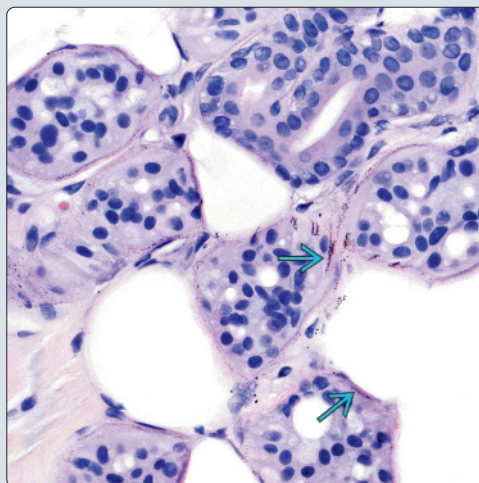
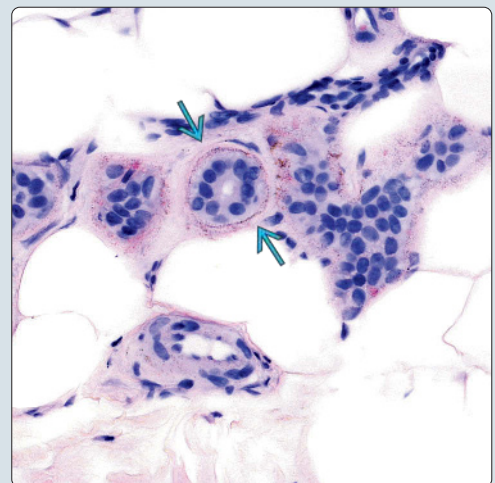
- Tattoo

**Bluish Discoloration of Argyria**

(Left) This patient took herbal supplements containing silver every spring and fall for 15 years. Note the perioral blue discoloration of her skin [E]. (Right) Silver granules preferentially deposit around sweat glands [E].

**Silver Granules Surrounding Sweat Glands****Brown to Black Fine Pigment Around Eccrine Glands**

(Left) Dark brown to black, fine, particulate matter is seen outlining the basement membrane zone of eccrine glands [E]. (Right) Both localized and generalized argyria share the same histology with fine, dark brown pigment [E] surrounding sweat glands.

**Brown to Black Fine Pigment Surrounding Eccrine Glands**



**TERMINOLOGY****Definitions**

- Pigmentation of skin that results from prolonged exposure to silver

**ETIOLOGY/PATHOGENESIS****Contact Exposure to Silver Salts**

- Silver deposits directly in skin (localized argyria)
  - Occupational exposure: Silver mining, photographic processing, metal alloy manufacturing
  - Topical medications: Silver sulfadiazine creams used for wounds, eye drops
  - Other: Dental amalgam containing silver, acupuncture needles, silver earrings

**Systemic Ingestion of Silver Salts**

- Silver deposits diffusely throughout skin (generalized argyria): Gray pigmentation occurs primarily in sun-exposed skin, thought to be due to photo-induced reduction to elemental silver
  - Silver deposition may also stimulate melanogenesis in presence of light
  - Occupational: Ingestion of dust during processing of silver
  - Medicinal: Colloidal silver dietary supplements

**CLINICAL ISSUES****Presentation**

- Blue to slate-gray discoloration of skin
- Occurs most commonly on sun-exposed areas of skin, although nail and mucosa can also be affected
- Usually appears in years following exposure

**Treatment**

- No effective treatment
- Topical hydroquinone, dermabrasion, chelating therapy, Q-switched 1064 nm Nd:YAG laser have been tried
- Sun protection to prevent further pigmentation may be important

**Prognosis**

- Argyria is permanent and usually irreversible, but not dangerous
- Patient may experience systemic effects from silver toxicity

**MICROSCOPIC****Histologic Features**

- Minute brown-black granules in dermis favoring sweat glands (especially in linear fashion outlining basement membrane zone of eccrine glands)
- Granules may also be found concentrated in perifollicular sheath, nerve, capillary walls, and elastic fibers
- Spares epidermis

**DIFFERENTIAL DIAGNOSIS****Histopathologic**

- Tattoo

- Clumps of fine, pigmented particulate concentrated around blood vessels in superficial to middermis; may be intracellular within macrophages or extracellular
- Blue nevus
  - Several variants exist: Most commonly shows dendritic melanocytes in sclerotic stroma with heavy pigmentation
    - Epidermis is spared
    - Dark granules are absent
- Ochronosis
  - Yellow to brown banana-shaped fibers in dermis
- Minocycline hyperpigmentation
  - 3 subtypes with different histologic patterns
    - Pigment-laden macrophages are found in Types 1 and 2, which stain with Perls and/or Fontana-Masson stains
    - Type 3 demonstrates only increased melanin in basal layer of epidermis
- Amiodarone hyperpigmentation
  - Yellow-brown lipofuscin granules inside macrophages; granules stain positively with periodic acid-Schiff stain
- Antimalarial hyperpigmentation
  - Coarse, yellow-brown pigment granules within macrophages and extracellularly in superficial dermis; granules are larger than fine silver particulate of argyria
  - Background of hemosiderin often (hydroxychloroquine pigmentation preferentially occurs in areas of previous ecchymosis)

**Clinical**

- Diagnosis is not difficult if thorough history is obtained
- If localized
  - Tattoo
  - Blue nevus
  - Ochronosis
  - Regressed melanoma
- If generalized
  - Drug-induced hyperpigmentation: Minocycline, amiodarone, antimalarials
  - Addison disease
  - Hemochromatosis
  - Cyanosis
  - Diffuse melanosis in metastatic melanoma

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# Minocycline Deposition

## KEY FACTS

### TERMINOLOGY

- Drug-induced hyperpigmentation

### CLINICAL ISSUES

- Hyperpigmentation of skin from long-term minocycline use and separated into 3 types
  - Type I (blue-black)
    - Occurs in scars, sites of prior inflammation or acne
  - Type II (blue-gray)
    - Occurs on anterior shins
  - Type III ("muddy brown")
    - Generalized appearance in photodistribution

### MICROSCOPIC

- Pigment deposition can be variable
  - Can present as flocculent brown, golden-brown or brown to black granules
  - Pigments is seen within dendritic cells, fibroblasts or macrophages

- Also seen around sweat glands and microvasculature

### TOP DIFFERENTIAL DIAGNOSES

- Other drugs
  - Chloroquine
  - Hydroxychloroquine
  - Quinacrine
  - Amiodarone
  - Clofazimine
  - Zidovudine
  - Chlorpromazine
  - Thioridazine
  - Imipramine
- Postinflammatory hyperpigmentation due to nondrug related causes (inflammation, trauma, etc.)
- Nevus (blue nevus, combined nevus, recurrent nevus), melanoma or part of syndrome like Carney complex

Type II Minocycline on Anterior Shins

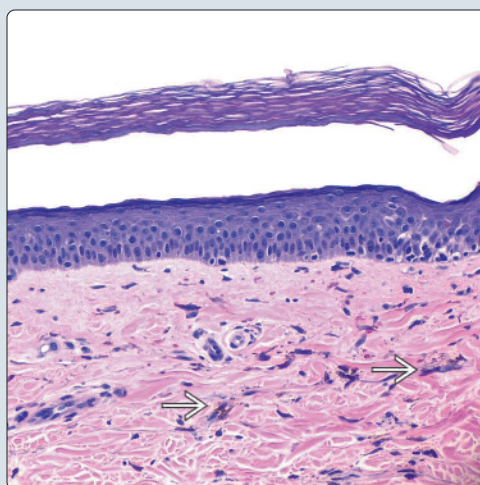


Type I Minocycline Deposition in Acne Scars

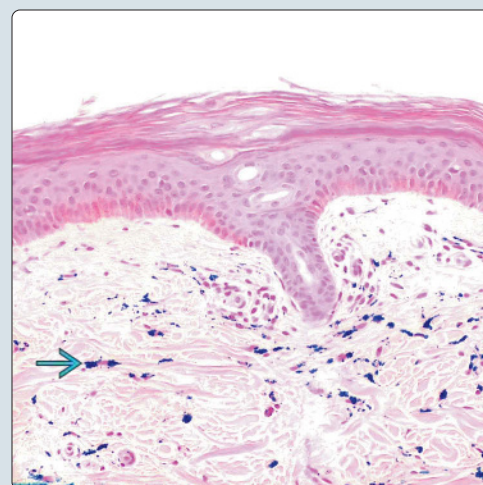


(Left) Clinical image shows minocycline hyperpigmentation represented by the blue-black to slate-gray appearance of the bilateral anterior shins (type II). (Courtesy of E. Lilly, MD.) (Right) Blue-gray pigmentation (type I) of acne scars from chronic use of minocycline. (Courtesy A. Lipworth, MD.)

Minocycline Deposition



Prussian Blue Positivity in Minocycline Deposition



(Left) Pigment deposition in dermal dendritic cells in a patient who had been taking minocycline long term is shown. (Courtesy L. Cohen, MD.) (Right) Pigment (iron) deposition, highlighted by a Prussian blue special stain, is shown in dermal dendritic cells in a patient who had been taking minocycline long term. (Courtesy L. Cohen, MD.)

## TERMINOLOGY

### Definitions

- Drug-induced hyperpigmentation

## CLINICAL ISSUES

### Presentation

- Presents as hyperpigmented skin in 3 types
  - Type I (blue-black)
    - Occurs in scars, sites of prior inflammation or acne
  - Type II (blue-gray)
    - Occurs on anterior shins
  - Type III ("muddy brown")
    - Generalized appearance in photodistribution

### Treatment

- Options, risks, complications
  - Observation vs. Q-switch laser

### Prognosis

- Relatively benign course, can resolve spontaneously in some individuals, but often has protracted course

## MICROSCOPIC

### Histologic Features

- Pigment deposition can be variable
  - Can present as flocculent brown, golden-brown or brown to black granules
  - Pigments is seen within dendritic cells, fibroblasts or macrophages
    - Also seen around sweat glands and microvasculature

## ANCILLARY TESTS

### Histochemistry

- Perls Prussian blue stain (type I positive, type II positive)
- Fontana Masson (type I positive sometimes, type II positive, type III positive)

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Drug-induced hyperpigmentation
  - Can be challenging as it can leave deposits around eccrine units, in fibroblasts, or macrophages depending upon medication
- Postinflammatory hyperpigmentation
  - Hemosiderin-laden, or melanin-laden macrophages in dermis are not uncommon after inflammatory or traumatic process
- Nevus (blue nevus, combined nevus, recurrent nevus), melanoma, or part of syndrome like Carney complex
  - Pigmented nevus or dendritic cells, which stain positive for melanin markers, S100

### Clinical

- Other drugs (chloroquine, hydroxychloroquine, quinacrine, amiodarone, clofazimine, zidovudine, chlorpromazine, thioridazine, imipramine)
  - Clinical history is most helpful along with areas or distribution and clinical appearance

- Postinflammatory hyperpigmentation due to nondrug related causes (inflammation, trauma, etc.)
  - Usually occurs during and after resolution stage of inflammatory condition
- Nevus (blue nevus, combined nevus, recurrent nevus), melanoma or part of syndrome like Carney complex
  - Tend to be limited to solitary site anatomically
- Heavy metals (silver, gold, bismuth)
  - Clinical history is most helpful along with areas or distribution and clinical appearance
- Hemosiderosis
  - Often history of iron overload can be found
- Ecchymosis
  - Often occurs in elderly, frequently due to inadvertent trauma

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Presents as hyperpigmentation (blue-black, blue-gray or "muddy brown") involving either scars, sites of prior inflammation or acne, on shins, or in photodistribution

### Pathologic Interpretation Pearls

- Pigment deposition can be variable presenting as flocculent brown, golden-brown, brown to black granules within dendritic cells, fibroblasts or macrophages around sweat glands and microvasculature

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# Monsel Reaction

## KEY FACTS

### TERMINOLOGY

- Hemostatic solution (20% aqueous ferric subsulfate) sometimes used after procedure that can cause unusual dermal pigmentation and histiocytic proliferation in dermis

### ETIOLOGY/PATHOGENESIS

- Clinical use of Monsel solution after punch or shave biopsy can cause permanent discoloration of skin

### CLINICAL ISSUES

- Occurs much less commonly now that clinicians are more educated on side effects of Monsel

### MICROSCOPIC

- Spindle-shaped and polyhedral macrophages ± giant cells that can stream off epidermis or be more deeply situated
  - Cytologic atypia and occasional mitotic figures can be seen

- Slightly refractile dark black or brown pigment deposited freely within dermis, within collagen fibers, and within reactive macrophages
  - Larger black encrustations can sometimes form
  - Pigment is typically darker in color than hemosiderin and is not as refractile
- Dermal scar from prior biopsy procedure may or may not be identifiable

### ANCILLARY TESTS

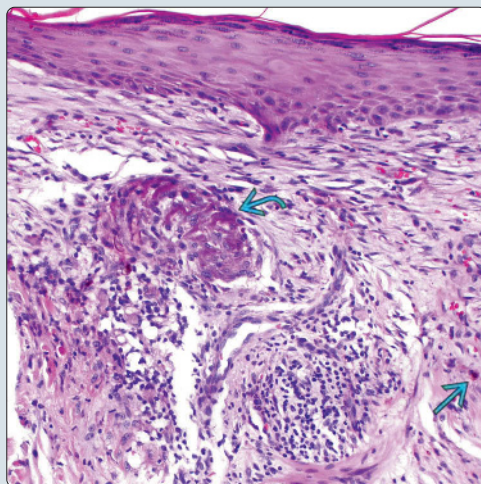
- Iron stains (Perls, etc.) will strongly highlight Monsel solution

### TOP DIFFERENTIAL DIAGNOSES

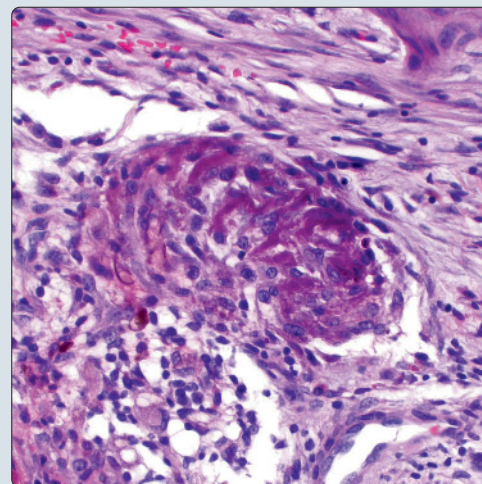
- Melanoma
- Atypical fibroxanthoma
- Squamous cell carcinoma

**Spindled Macrophages With Brown Pigment**

(Left) Spindle-shaped macrophages are seen streaming off the epidermis with underlying macrophages containing brown pigment [E]. There is also brown pigment freely within the dermis [E]. (Right) High-power view shows macrophages containing brown pigment that is typically darker than hemosiderin and is not as refractile. Iron stains would strongly stain this pigment.

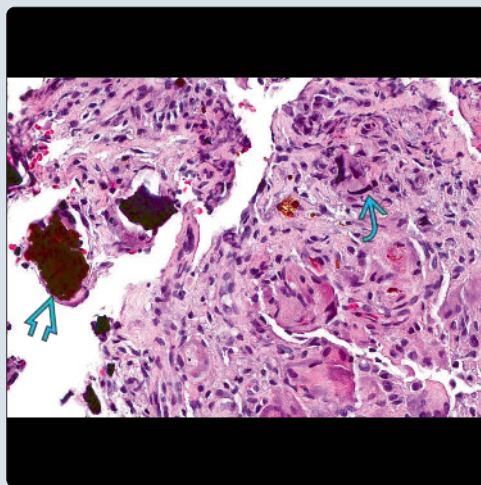


**High-Power View of Brown Monsel Pigment**

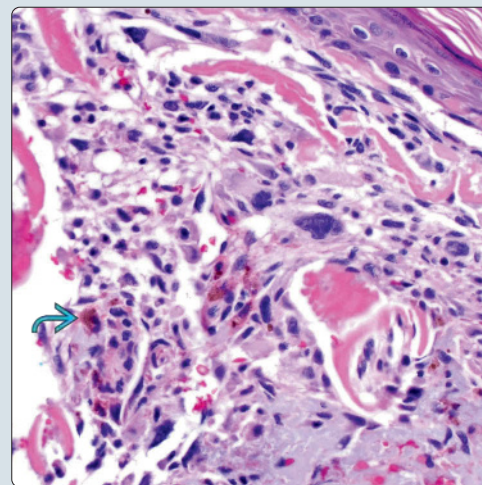


**Encrustations and Pigment Within Giant Cells**

(Left) This image demonstrates large brown-black encrustations [E] as well as brown-black pigment within giant cells [E] and macrophages and freely within the dermis. (Right) This case of atypical fibroxanthoma demonstrated abundant hemosiderin [E] deposition. Note how the pigment appears lighter than Monsel solution and was much more refractile under the microscope. There were also no encrustations and no history of use of Monsel solution.



**Atypical Fibroxanthoma With Abundant Hemosiderin Deposition**



## TERMINOLOGY

### Synonyms

- Monsel tattoo

### Definitions

- Hemostatic solution (20% aqueous ferric subsulfate) sometimes used after procedure that can cause unusual dermal pigmentation and histiocytic proliferation in dermis

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- Clinical use of Monsel solution after punch or shave biopsy can cause permanent discoloration of skin
  - Iron sesquioxide has been reported to create similar clinical and histopathologic reaction

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Occurs much less commonly now that clinicians are more educated on side effects of Monsel
    - However, clinician and pathologist should still both be educated since Monsel is still used in some practices
    - Fibrohistiocytic responses do not occur in all cases

### Presentation

- Appears as irregular macular area of hyperpigmentation within scar
- Typically brown in color

### Treatment

- None typically needed
  - Lesions may be biopsied to rule out possibility of melanoma, atypical nevus, or other malignancy
- Excision can remove pigment

### Prognosis

- Excellent
  - Fibrohistiocytic proliferation is entirely benign

## MICROSCOPIC

### Histologic Features

- Epidermis may exhibit mild reactive changes or be unremarkable
  - Mild hyperkeratosis, parakeratosis, or irregular acanthosis have been reported
  - Rare reports of transepidermal elimination with
    - Significant acanthosis and central channel of Monsel pigment with surrounding reactive fibrohistiocytic proliferation, hemorrhage, and necrotic tissue
- Dermal changes are much more pronounced and include
  - Spindle-shaped and polyhedral macrophages ± giant cells that can stream off epidermis or be more deeply situated
    - Cytologic atypia and occasional mitotic figures can be seen
  - Slightly refractile dark black or brown pigment deposited freely within dermis, within collagen fibers, and within reactive macrophages
    - Larger black encrustations can sometimes form

- Dermal scar from prior biopsy procedure may or may not be identifiable
- Transepithelial elimination of Monsel pigment has been reported

### Cytologic Features

- Pigment is typically darker in color than hemosiderin and is not as refractile

## ANCILLARY TESTS

### Histochemistry

- Iron stains (Perls, etc) will strongly highlight Monsel solution

### Immunohistochemistry

- Histiocytic markers (CD163, CD68) should be positive in reactive fibrohistiocytic cells

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Melanoma
  - Melanin pigment is nonrefractile (vs. Monsel solution)
  - Absence of prior biopsy or use of Monsel solution
  - Encrustations absent
  - Dermal scar should not be present
  - In difficult cases, immunohistochemical staining should help distinguish
    - S100, Melan-A, SOX10, others
- Atypical fibroxanthoma
  - Hemosiderin deposition can sometimes be seen within atypical fibroxanthomas
  - Absence of prior biopsy or use of Monsel solution
    - Most important differentiating factor
  - Encrustations typically absent
  - Dermal scar should not be present
- Squamous cell carcinoma (spindle cell variant)
  - Absence of prior clinical application of Monsel solution
  - Hemosiderin deposition typically absent
  - Dermal scar typically not present
  - In difficult cases, immunohistochemistry can help distinguish
    - Most cases are cytokeratin (+) or p63(+)

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# Calciophylaxis

## KEY FACTS

### TERMINOLOGY

- Calcification of small and medium-sized vessels in deep dermis and subcutis that can lead to cutaneous ulceration and necrosis

### CLINICAL ISSUES

- Violaceous plaque in retiform morphology in extremities or trunk
- Very painful lesions
- Rare entity, but usually occurs in association with end-stage renal disease (ESRD) or recent renal transplant patients

### MICROSCOPIC

- Necrosis of dermis &/or epidermis
- Calcification of media in small arteries located at deep dermis and subcutis
- Calcification of soft tissue

### TOP DIFFERENTIAL DIAGNOSES

- Calcinosis cutis

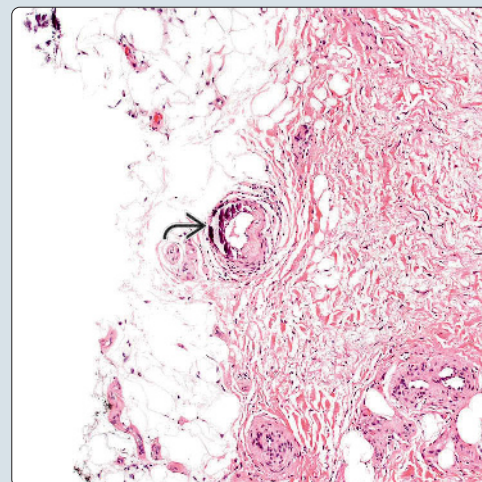
- Calcification in dermis
- Usually not involving vessels
- Pancreatic panniculitis
  - Calcification in subcutis involving degenerated fat but not vessels
- Gout
  - Urate crystals in dermis or subcutis
  - Older lesion; calcification in dermis or subcutis but calcification spares vessels
- Oxalosis
  - Oxalate crystals in dermis or subcutis
  - In livedo reticularis, crystals found in blood vessels
- Pseudogout
  - Calcium pyrophosphate dihydrate crystals
  - Usually at joints and rarely in subcutis

**Necrotic Painful Induration**

(Left) A necrotic, exquisitely sensitive area of induration presented on the inner thigh of this dialysis patient. Biopsy confirmed calciophylaxis. (Right) Calciophylaxis demonstrates medium-sized vessels at the junction of dermis and subcutis involved by calcification [2].

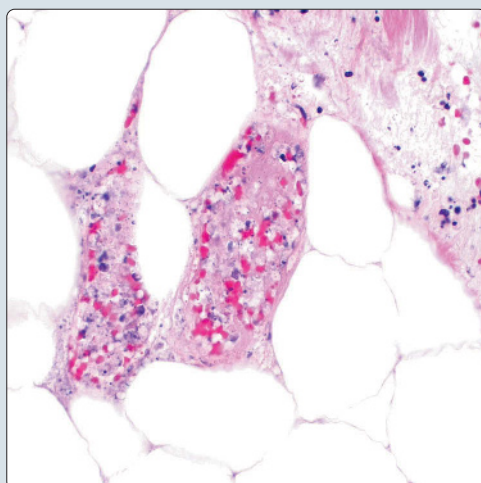


**Calcification of Medium-Sized Vessel in Subcutis**

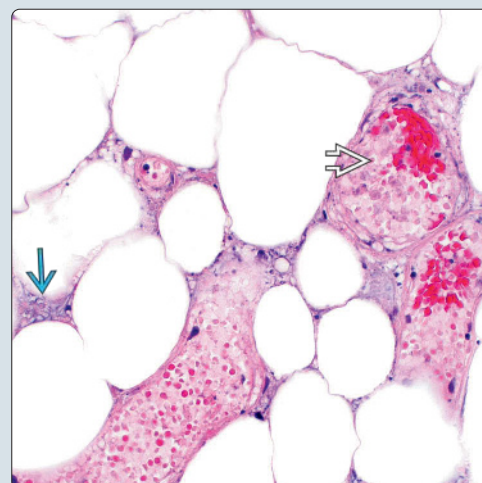


**Microthrombi in Calciophylaxis**

(Left) Small capillaries in the subcutis demonstrate luminal thrombi and microcalcification in calciophylaxis (Right) Microcalcifications are seen in extravascular subcutaneous spaces in calciophylaxis [2]. Thrombi occlude small capillaries [3].



**Extravascular Calcium in Calciophylaxis**





## TERMINOLOGY

### Definitions

- Calcification of small and medium-sized vessels in deep dermis and subcutis that can lead to cutaneous ulceration and necrosis

## ETIOLOGY/PATHOGENESIS

### Unclear

- Possibly caused by elevation of calcium and phosphorus
- Also seen in hypercoagulable state

### Association

- End-stage renal disease (ESRD) patients who are on dialysis or have recently had renal transplant
- Secondary hyperparathyroidism, hyperphosphatemia, calcium salt intake, and vitamin D therapy

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Rare but usually occurs in association with ESRD or recent renal transplant patients
  - Can rarely occur in patients without ESRD (nonuremic calciophylaxis)
- Age
  - Can affect all ages
- Sex
  - F > M

### Presentation

- Painful retiform purpura with ulceration on trunk or extremities
- May be complicated by infection of gangrenous tissue

### Treatment

- Drugs
  - Antibiotics
  - Sodium thiosulfate
- Others
  - Dialysis
  - Wound care
  - Urgent parathyroidectomy

### Prognosis

- Very poor with potential for rapid progression
  - Considered medical emergency

## MICROSCOPIC

### Histologic Features

- Necrosis of dermis &/or epidermis; secondary to ischemia
- Calcification of media in small arteries and capillaries located at deep dermis and subcutis
- Calcification of soft tissue
- Thrombosis of small vessels in subcutis

## ANCILLARY TESTS

### Metabolic Work-Up

- Serum calcium and phosphorus levels may help determine cause

## DIFFERENTIAL DIAGNOSIS

### Calcinosis Cutis

- Calcification in dermis
- Usually not involving vessels
- Calciophylaxis actually considered subtype

### Pancreatic Panniculitis

- Calcification in subcutis involving degenerated fat but not vessels
- Enzymatic fat necrosis leads to ghost cells
- Neutrophilic infiltrate with nuclear dust

### Gout

- Urate crystals in dermis or subcutis
- In formalin, amorphous pink areas surrounded by foreign body giant cells
- In alcohol, brown, needle-shaped crystals
- Older lesion; calcification in dermis or subcutis but calcification spares vessels

### Oxalosis

- Oxalate crystals in dermis or subcutis
- Yellow or brown deposits with foreign body giant cells
- In livedo reticularis, crystals found in blood vessels

### Pseudogout

- Calcium pyrophosphate dihydrate crystals
- Usually at joints and rarely in subcutis
- More macrophages and histiocytes

### Calcifications From Other Cutaneous Lesions

- Calcifications in pilar cysts, basal cells carcinoma, syringomas, and pilomatricomas
- Usually residual neoplasm around calcification
- Not at intima of vessels

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Notify clinician about result as soon as possible

### Pathologic Interpretation Pearls

- Make sure that calcification is in intima of arteries
  - Perform multiple deeper sections to find these calcifications
  - Ask for multiple biopsies to search for this if clinically indicated

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## Ochronosis

## KEY FACTS

## TERMINOLOGY

- Ochronosis: Discoloration of collagen-containing tissues due to homogentisic acid (HGA) deposition resulting from
  - Genetic lack of homogentisic acid oxidase (HGO) resulting in alkaptonuria (AKU)
  - HGO inhibition by exogenously applied substances, most notably topical hydroquinone

## CLINICAL ISSUES

- Blue-gray macular discoloration of sclera and skin overlying cartilage, such as pinna of ear and ala of nose in AKU
- Blue-gray macular or maculopapular discoloration of sun-exposed areas of face, such as central facial convexity
- AKU may manifest with joint or back pain, heart murmur, &/or urinary obstruction

## MICROSCOPIC

- Pigment incontinence causing melanin in dermis

- Brownish-yellow "ochre," banana-shaped fibers in superficial dermis

## ANCILLARY TESTS

- Dermoscopy shows irregular, brown-gray, globular, annular, and arciform structures and granules
- Reflectance confocal microscopy shows hyporefractile, banana-shaped spaces

## TOP DIFFERENTIAL DIAGNOSES

- Postinflammatory hyperpigmentation
- Melasma
- Substance-induced hyperpigmentation
  - Minocycline
  - Amiodarone
  - Silver (argyria)
- Dermatitis papulosis nigra
- Nevus of Ota

Macular Skin Discoloration

(Left) This mild (stage 1) case of ochronosis shows predominantly macular pigmented skin discoloration of the face with only focal subtle pinpoint papule formation. (Right) This patient shows more prominent (stage 2) skin discoloration and textural changes of the face, including hyperchromic, caviar-like papules and macular hyperpigmentation.

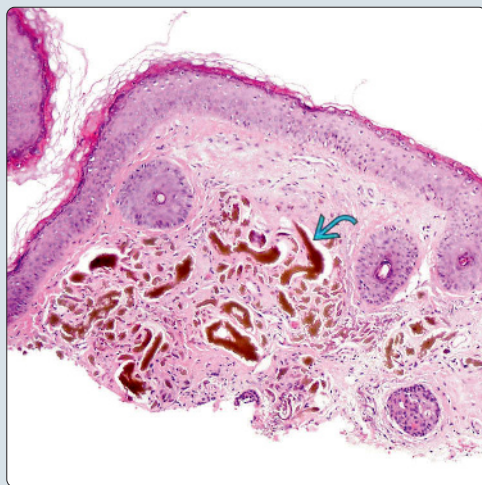


Hyperchromic Papules and Macular Hyperpigmentation

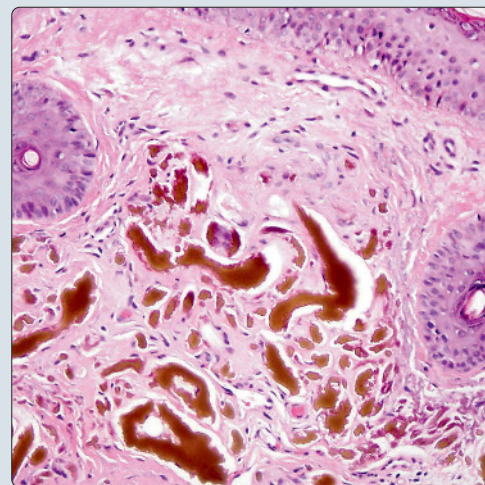


Brown, Banana-Shaped "Ochre" Pigment

(Left) "Ochre" pigmented fibers are yellow to brown in color and often demonstrate a banana shape when displacing collagen in the dermis. (Right) Banana-shaped ochre pigmented fibers displace dermal collagen in cases of ochronosis.



"Ochre" Pigment Displacing Dermal Collagen



**TERMINOLOGY****Synonyms**

- Alkaptonuria (AKU): Alkaptonuric ochronosis, black urine disease, or alkaptonuric rheumatism
- Exogenous ochronosis: Iatrogenic ochronosis

**Definitions**

- Discoloration of collagen-containing tissues due to homogentisic acid (HGA) deposition resulting from
  - Genetic lack of homogentisic acid oxidase (HGO) resulting in AKU
  - HGO inhibition by exogenously applied substances, most notably topical hydroquinone

**ETIOLOGY/PATHOGENESIS****Alkaptonuria**

- Autosomal recessive genetic disease in which there is lack of HGO activity due to mutation of *HGD* gene on chromosome 3q
- HGA builds up in body and deposits in connective tissues (cartilage, tendons, sclerae)
- HGA oxidizes to benzoquinones, which form melanin-like polymers called ochre pigment, thus causing darkening of tissue at sites of HGA deposition and darkening of urine when left standing
- Over years, HGA deposition causes destruction of cartilage, tendons, ligaments, heart valves, and muscles, due to any of several possible theories
  - HGA is chemical irritant, inducing inflammation directly or secondary to its oxidation, eventually causing more rapid degeneration of joints
  - Ochre pigment polymers or HGA itself bind to connective tissue macromolecules, altering structural integrity of tissue
  - Inhibition of lysyl hydroxylase, which is required for connective tissue cross-linking through currently unclear mechanism

**Exogenous Ochronosis**

- Most commonly induced by topical hydroquinone in skin lightening creams used to treat melasma
- Other implicated products are those containing resorcinol, phenol, mercury, and picric acid, as well as antimalarial drugs
- These compounds may inhibit HGO, leading to accumulation of HGA in papillary dermis and ochre pigment formation and deposition

**CLINICAL ISSUES****Epidemiology**

- Incidence
  - AKU
    - Prevalence: Rare (1 per million), reflecting autosomal recessive inheritance
  - Exogenous ochronosis
    - Prevalence: High in South Africa and quite uncommon in United States
- Age
  - AKU

- Symptoms start after age 30; mean age at diagnosis: 56 years

- Exogenous ochronosis
  - No significant age predilection
- Sex
  - AKU
    - Slight male predilection
  - Exogenous ochronosis
    - Female predilection among persons using hydroquinone creams
- Ethnicity
  - AKU
    - Predilection in persons of Slovakian and Dominican descent
  - Exogenous ochronosis
    - Predilection for darker skinned individuals

**Presentation**

- Genetic ochronosis
  - Chief complaint most frequently skin or eye discoloration, although joint and back pain are common initial complaints as well
  - Positive family history of disease may exist but is not required for diagnosis
  - Physical exam findings
    - Blue-gray macular discoloration of sclera and skin of pinna of ear, ala of nose, face, palms and soles, nail beds, axillary and inguinal areas
    - Heart murmur if valvular pathology present
    - Decreased range of motion in large joints and lumbar spine; pain in joints and back without warmth or erythema
    - Cerumen, sweat, and breast milk may be dark
  - Review of systems
    - Angina and dyspnea on exertion may be present if coronary artery calcification is significant
    - Flank pain if urinary obstruction due to stone is severe or if there is pyelonephritis
- Exogenous ochronosis
  - Chief complaint of color and texture changes in sun-exposed regions of face (especially zygomatic areas and temples), sides and back of neck, and extensor surfaces of limbs
  - History of either topical or systemic use of drug known to cause exogenous ochronosis
  - May have concurrent melasma, which hydroquinone was prescribed to treat
  - Skin findings depend on disease stage
    - Stage 1: Gray-brown and blue-gray hyperpigmented macules
    - Stage 2: Pinpoint, hyperchromic, caviar-like papules plus macular hyperpigmentation
    - Stage 3: Nodules due to granuloma formation

**Laboratory Tests**

- Urine HGA level
  - Elevated HGA levels in urine is diagnostic of AKU
  - Normal in exogenous ochronosis
- Urine color darkens upon exposure to air or reducing agents in AKU but not in exogenous ochronosis



**Treatment**

- AKU
  - No FDA-approved drug therapy yet
  - Regular surveillance for joint, renal, and cardiovascular complications
  - Surgery may be indicated for tendon and ligament rupture, severe joint degeneration, cardiovascular disease, nephrolithiasis
  - Nitisinone shown to reduce urinary and plasma HGA but did not improve clinical outcomes of joint range of motion and musculoskeletal function
  - Vitamin C supplementation and low protein diet have not been shown to be effective at reducing serum HGA
  - Joint and back pain management with analgesics
- Exogenous ochronosis
  - Discontinuation of contributing drug
  - Retinoic acid, sunscreen, nonhydroquinone depigmentation cream, topical corticosteroids helpful in some
  - Skin discoloration may be removed by laser (carbon dioxide or quality-switched alexandrite) or dermabrasion therapy

**Prognosis**

- AKU
  - Chronic and progressive disease with no cure
  - Near normal life expectancy but significant morbidity from disease
  - Musculoskeletal involvement begins during 4th decade of life in most patients
  - Cardiovascular involvement occurs during 6th decade of life on average
  - Renal stone occurs on average at 64 years but intrinsic renal failure uncommon
  - More rapidly progressive in men than women
- Exogenous ochronosis
  - Cosmetic issue with no effect on health

**MACROSCOPIC****General Features**

- Blue-gray macules and sometimes papules or nodules

**MICROSCOPIC****Histologic Features**

- Common to AKU and exogenous ochronosis
  - Brownish-yellow "ochre," banana-shaped fibers in papillary dermis, with infiltration of collagen and elastic fibers, along with collagen and elastic fiber disorganization and degeneration
  - Pigment incontinence with increased melanin in dermis and macrophages
  - No significant findings in epidermis
- Exogenous ochronosis only
  - Colloid milia or sarcoidal granulomas, both containing pigment, may be found in stages 2 and 3 disease, respectively
  - Transepidermal or transfollicular elimination of ochronotic pigment may be seen

**ANCILLARY TESTS****PCR**

- Sequencing of *HGD* gene shows homozygous or compound heterozygous mutated *HGD* genes in AKU

**Reflectance Confocal Microscopy**

- Hyporefractile, banana-shaped spaces

**Dermoscopy**

- Irregular, brown-gray, globular, annular, and arciform structures and granules

**DIFFERENTIAL DIAGNOSIS****Postinflammatory Hyperpigmentation**

- Melanin incontinence without ochronotic deposits

**Melasma**

- Increased melanin present in epidermis
- Exogenous ochronosis may be superimposed on melasma treated with hydroquinone cream

**Substance-Induced Hyperpigmentation**

- Minocycline
  - Deposits in subcutaneous fat in addition to dermis
  - Golden-brown to black granules in macrophages
- Amiodarone
  - Yellow-brown granules and lipofuscin in macrophages
- Silver (argyria)
  - Silver deposits appear white on dark field

**Dermatosis Papulosis Nigra**

- Resembles seborrheic keratosis and shows hyperpigmented basal epidermal layer

**Nevus of Ota**

- Usually unilateral, while ochronosis is usually bilateral

**DIAGNOSTIC CHECKLIST****Clinically Relevant Pathologic Features**

- Exogenous ochronosis
  - History of use of drug that induces ochronosis, especially topical hydroquinone

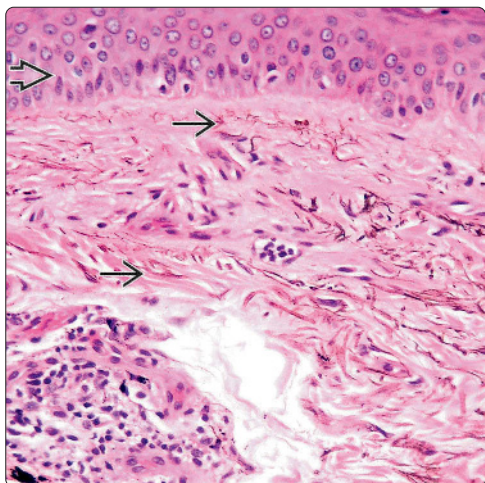
**Pathologic Interpretation Pearls**

- Pigment incontinence causing melanin in dermis
- Brownish-yellow "ochre," banana-shaped fibers in superficial dermis

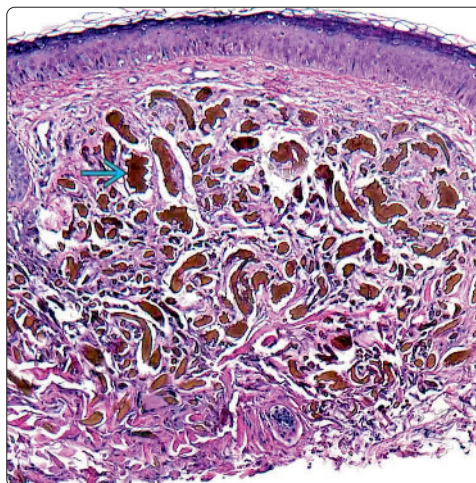
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Scattered, Pigmented "Ochre" Fibers

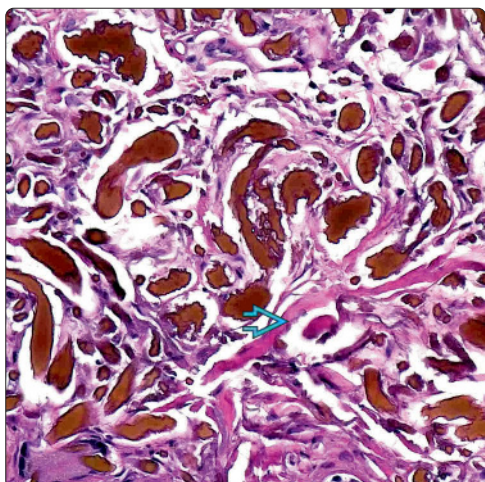


Banana-Shaped "Ochre" Pigment

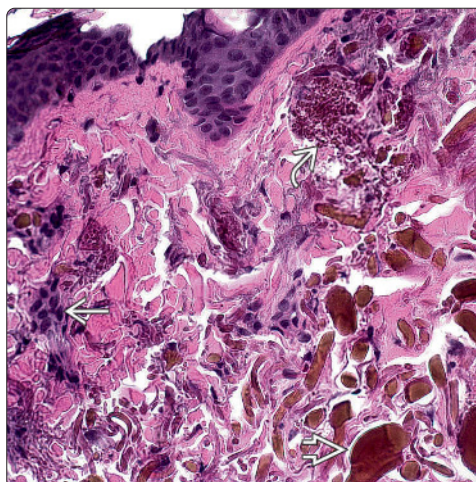


(Left) Ochronosis demonstrates brownish-yellow "ochre" pigmented fibers in the papillary dermis. This subtle example shows scattered pigmented "ochre" fibers interspersed amid collagen and elastic fibers within the papillary dermis. No epidermal pigment is seen. (Right) This case of exogenous ochronosis demonstrates more abundant "ochre" pigmented fibers that fill the reticular and papillary dermis. There is some distortion of the collagen and elastic fibers.

Brown to Yellow Pigmented Fibers

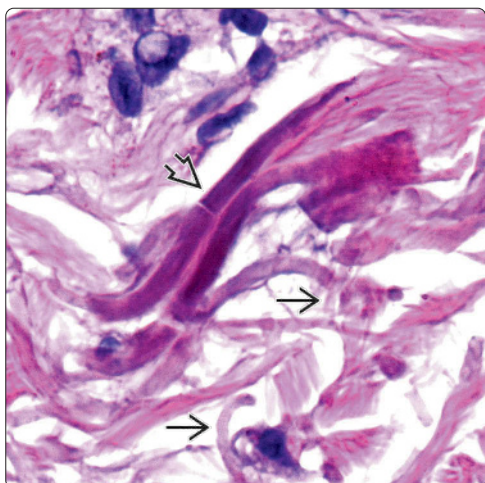


Histiocytes Adjacent to "Ochre" Fibers

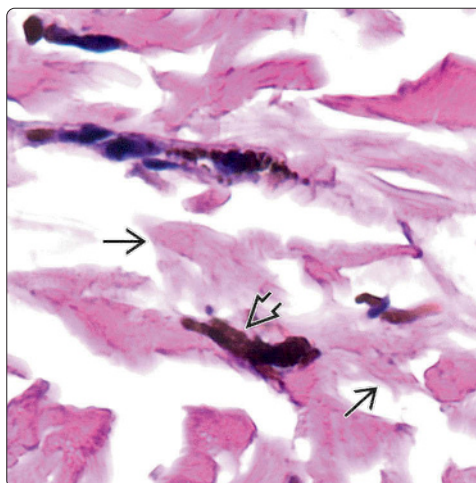


(Left) Closer examination of the previous case reveals distortion of the normal collagen architecture due to the presence of the dense aggregates of often banana-shaped, brown to yellow "ochre" pigmented fibers. (Right) This example of ochronosis shows the presence of histiocytes within the papillary dermis located adjacent to the pigmented "ochre" fibers. There are also abundant intracellular and extracellular granular deposits evident in this case.

"Ochre" Pigment Displacing Collagen



Extracellular Granular Deposits of "Ochre"



(Left) This high-power view of ochronosis nicely displays the brownish-yellow "ochre" banana-shaped pigmented fibers with associated disorganization and displacement of dermal elastic fibers and collagen fibers. (Right) High-power examination of ochronosis shows variably shaped, brownish-yellow "ochre" fibers with extracellular granular deposits. There is some distortion of adjacent collagen fibers.



## Lipoid Proteinosis

## KEY FACTS

## ETIOLOGY/PATHOGENESIS

- Mutations in *ECM1* gene

## CLINICAL ISSUES

- Hoarseness
- Thickened lip and tongue with cobblestone appearance
- Diffusely thickened and waxy skin with yellowish discoloration
- String of pearls sign on eyelid margin
- Verrucous papules, plaques, and nodules on knees, elbows, and hands
- Risk of seizures

## IMAGING

- Bilateral, intracranial, sickle-shaped suprasellar calcifications in temporal lobe

## MICROSCOPIC

- Diffuse deposition of amorphous, hyaline-like material in dermis

## TOP DIFFERENTIAL DIAGNOSES

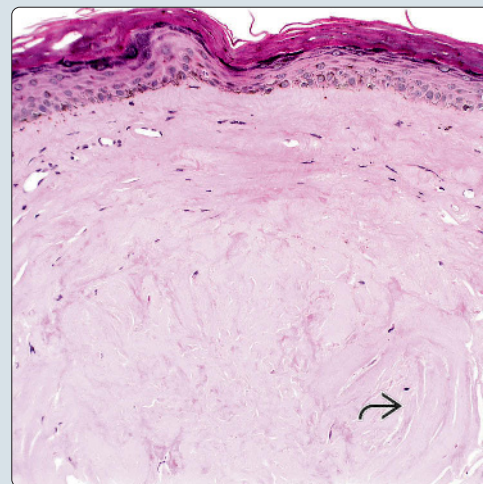
- Erythropoietic protoporphyria
  - Increased erythrocyte and plasma protoporphyrin levels; fecal protoporphyrin excretion may be increased
- Systemic amyloidosis
  - Petechiae and ecchymoses are common clinical features
  - Biopsies are Congo red stain (+)
- Juvenile hyaline fibromatosis/infantile systemic hyalinosis
  - Mutations in capillary morphogenesis protein-2
  - Painful swollen joint contractures and red pigmentation over bony prominences as well as gingival hypertrophy

String of Pearls on Eyelid Margin

(Left) Lipoid proteinosis clinically presents as a string of pearls with moniliform blepharosis or a characteristic row of beaded papules on the eyelid margin. (Courtesy R. Wang, MD, PhD.) (Right) Diffuse deposition of amorphous, hyaline-like material is shown in the dermis, periadnexal, and perivascular areas in a biopsy of lipoid proteinosis. Concentric layers are perpendicularly oriented to the basement membrane.

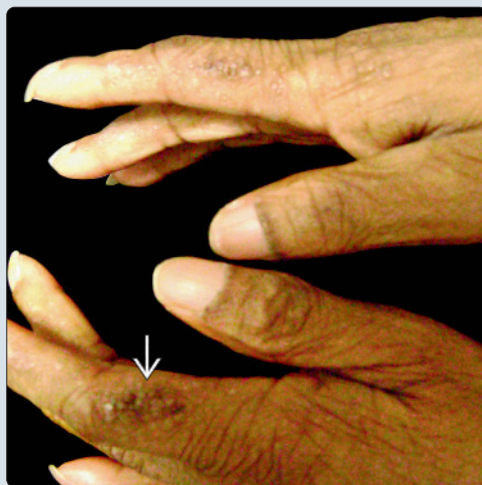


Hyaline-Like Material Deposition

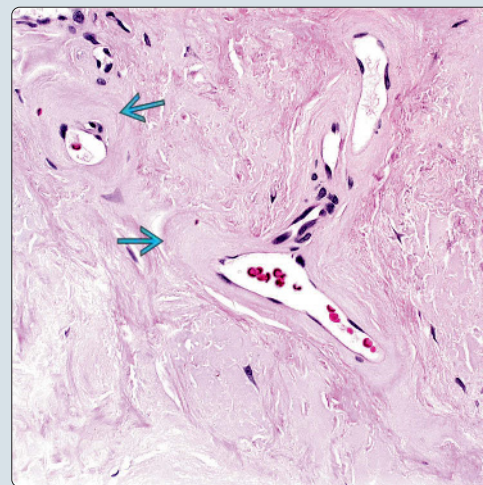


Lipoid Proteinosis on Hands

(Left) Clinically, lipoid proteinosis can present as verrucous papules on the hands. Similar papules, plaques, and nodules appear on the face, elbows, knees, axillae, and scrotum. (Courtesy R. Wang, MD, PhD.) (Right) Lipoid proteinosis demonstrates perivascular deposition of amorphous, hyaline-like material in the dermis. The deposits are PAS(+) and diastase resistant, suggesting neutral mucopolysaccharides.



Perivascular Deposition of Hyaline-Like Material





## TERMINOLOGY

### Synonyms

- Hyalinosis cutis et mucosae, Urbach-Wiethe disease

### Definitions

- Autosomal recessive genetic disorder caused by mutations in extracellular matrix protein 1 *ECM1* gene, resulting in amorphous, hyaline-like deposits in multiple organs, such as skin, oral mucosa, larynx, and brain

## ETIOLOGY/PATHOGENESIS

### Developmental Anomaly

- Loss-of-function mutations in *ECM1* gene

## CLINICAL ISSUES

### Epidemiology

- Ethnicity
  - Patients of European ancestry most commonly affected

### Presentation

- Skin
  - Vesicles and hemorrhagic crusts on face, mouth, and distal extremities in early stage; may leave permanent "ice pick" scarring
  - Row of beaded papules on eyelid margin (moniliform blepharosis); string of pearls sign
  - Diffusely thickened and waxy skin with yellowish discoloration
  - Verrucous papules, plaques, and nodules on knees, elbows, and hands
  - Papules, plaques, and nodules appear on face, axillae, and scrotum
- Hair
  - Patchy alopecia
- Oral mucosa
  - Pebbling of lip mucosa; cobblestone appearance
  - Infiltration of tongue and frenulum resulting in impaired mobility of tongue, speech, and gustation
  - Hypoplasia or aplasia of teeth, particularly upper incisors, premolars, and molars
- Upper airway
  - Weak cry and hoarseness (1st sign)
  - Infiltration of larynx, vocal cords, and surrounding structures may produce hoarseness, dysphagia, and airway obstruction
- Central nervous system
  - Seizures and learning difficulties

### Treatment

- Options, risks, complications
  - No known cure
- Surgical approaches
  - Excision of deposits or dermabrasion
- Drugs
  - Topical corticosteroid
  - Oral medications: Retinoid, D-penicillamine, and dimethyl sulfoxide; experimental

### Prognosis

- Stable or slowly progressive course, but with normal lifespan

## IMAGING

### Radiographic Findings

- Bilateral, intracranial, sickle-shaped suprasellar calcifications in temporal lobe

## MACROSCOPIC

### General Features

- Diffusely thickened yellowish waxy skin
- Verrucous and nonverrucous papules, plaques, and nodules

## MICROSCOPIC

### Histologic Features

- Diffuse deposition of amorphous hyaline-like material in upper dermis, periadnexal, and perivascular areas
  - Deposits are PAS(+) and diastase resistant, suggesting neutral mucopolysaccharides
  - Concentric layers, perpendicularly oriented to basement membrane, contain type II and IV collagen and laminin
- Hyperkeratosis and occasional papillomatosis in epidermis

## ANCILLARY TESTS

### Genetic Diagnostic Study

- Polymerase chain amplification and direct nucleotide sequencing of *ECM1* gene can confirm diagnosis

## DIFFERENTIAL DIAGNOSIS

### Erythropoietic Protoporphyrria

- Increased erythrocyte and plasma protoporphyrin levels; fecal protoporphyrin excretion may be increased

### Systemic Amyloidosis

- Petechiae and ecchymoses are common clinical features
- Biopsies are Congo red stain (+)

### Juvenile Hyaline Fibromatosis/Infantile Systemic Hyalinosis

- Mutations in capillary morphogenesis protein-2
- Painful swollen joint contractures and red pigmentation over bony prominences as well as gingival hypertrophy

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# Necrolytic Migratory Erythema

## KEY FACTS

### TERMINOLOGY

- Skin manifestation of glucagonoma syndrome
- Has been reported to be associated with other conditions
  - Other pancreatic neuroendocrine tumors, glucagon cell adenomatosis, intravenous glucagon administration, liver cirrhosis, malnutrition
- Similar to necrolytic acral erythema (NAE), acral necrolytic migratory erythema (NME)
  - Associated with hepatitis C and zinc deficiency
  - Predominantly occurs on lower extremities, primarily feet and toes
  - Similar histologically to NME

### CLINICAL ISSUES

- Trunk, groin, extremities, thighs, and buttocks are most frequently involved
- Annular or round erythematous or violaceous patches
- Vesicle or bulla formation with crusting after rupture
- Self-limited: Typically resolves within 2 weeks

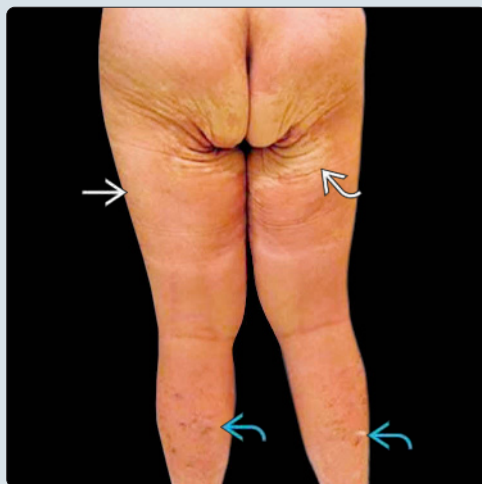
- Age > 40 yr (age distribution of glucagonoma)
- Rarely glucagonomas may arise in children
- Other systemic symptoms include
  - Glossitis, cheilitis
  - Diarrhea, steatorrhea
  - Elevated glucagon levels
  - Glucose intolerance, venous thrombosis
  - Weight loss, anemia, brittle nails, scotoma

### MICROSCOPIC

- Pale keratinocytes in upper epidermis with clear vacuoles and confluent parakeratosis
- $\pm$  necrosis, psoriasiform hyperplasia, spongiosis
- Significant necrosis may produce subcorneal or intraepidermal clefting
- May form neutrophilic pustules
- Usually superficial perivascular lymphocytic infiltrate  $\pm$  neutrophils

**Confluent Erythema**

(Left) Necrolytic migratory erythema shows confluent erythema with circinate borders and erosions at the site of rupture of flaccid bullae. (Courtesy PMPH-USA Publishing and the Univ. of Utah Dept. of Dermatology.) (Right) The most characteristic feature of necrolytic migratory erythema is pale, vacuolated keratinocytes within the superficial epidermis. (Courtesy S. Billings, MD.)

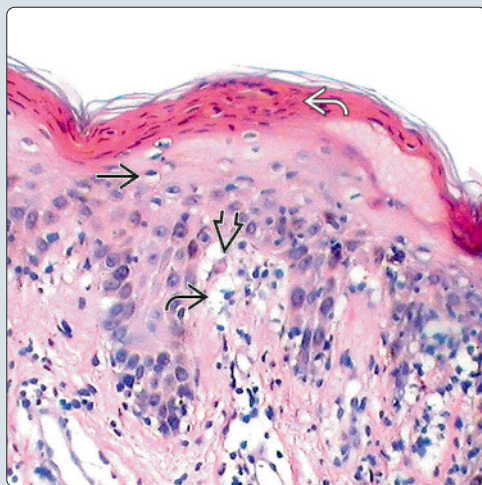


**Pale, Vacuolated Keratinocytes**



**Subepidermal Microvesiculation**

(Left) Closer inspection of a case of necrolytic acral erythema shows vacuolated keratinocytes with overlying confluent parakeratosis. Subepidermal microvesiculation is beginning secondary to keratinocyte necrosis. (Courtesy A. Halpern, MD.) (Right) In addition to pale keratinocytes, there is a mild superficial perivascular lymphocytic infiltrate. There are no neutrophils or dyskeratotic keratinocytes present. (Courtesy S. Billings, MD.)



**Mild Lymphocytic Infiltrate**



## TERMINOLOGY

### Abbreviations

- Necrolytic migratory erythema (NME)

### Definitions

- Skin manifestation of glucagonoma syndrome
  - Glucagon-secreting neuroendocrine tumor of pancreas
    - a.k.a. islet cell tumor
  - Presenting symptom of glucagonoma syndrome in 70% of cases
- Has been reported in other conditions
  - Other pancreatic neuroendocrine tumors
  - Glucagon cell adenomatosis
  - Intravenous glucagon administration
  - Liver cirrhosis
  - Malnutrition
- Necrolytic acral erythema (NAE), acral NME
  - Associated with hepatitis C and zinc deficiency
  - Predominantly occurs on lower extremities, primarily feet and toes
  - Similar histologically to NME

## CLINICAL ISSUES

### Epidemiology

- Age
  - > 40 yr (age distribution of glucagonoma)
    - Rarely glucagonomas may arise in children
    - NME has appeared in kids following iatrogenic glucagon therapy for hyperinsulinism
- Sex
  - More common in women

### Site

- Trunk, groin, extremities, thighs, and buttocks are most frequently involved

### Presentation

- Annular or round erythematous or violaceous patches
- Vesicle or bulla formation
  - Crusting after rupture
- Self-limited
  - Typically resolves within 2 weeks
- Other systemic symptoms include
  - Glossitis, cheilitis
  - Diarrhea, steatorrhea
  - Elevated glucagon levels
  - Glucose intolerance, venous thrombosis
  - Weight loss, anemia, brittle nails, scotoma

### Laboratory Tests

- Elevated glucagon levels are common

### Treatment

- Surgical approaches
  - Pancreaticoduodenectomy (Whipple procedure) or distal pancreatectomy
    - Remove tumor
  - Liver transplantation
    - Remove metastases
- Drugs

- Lanreotide or Octreotide
  - Long-acting somatostatin analogue
- Intravenous amino acid administration

### Prognosis

- Resolves with tumor removal

## MICROSCOPIC

### Histologic Features

- Pale keratinocytes in upper epidermis with clear vacuoles
- May have necrosis
  - Significant necrosis may produce subcorneal or intraepidermal clefting
    - May form neutrophilic pustules
- ± neutrophils within epidermis
- Usually superficial perivascular lymphocytic infiltrate ± neutrophils
- Individual dyskeratotic cells are uncommon
- Confluent parakeratosis
- ± psoriasiform hyperplasia, spongiosis

## DIFFERENTIAL DIAGNOSIS

### Histological

- Pellagra (niacin deficiency)
  - Scaly erythematous patches in areas of sun exposure
  - Bullae formation with subsequent desquamation
  - Psoriasiform hyperplasia with a pale upper epidermis
  - Focal parakeratosis
- Acrodermatitis enteropathica
  - Classically associated with zinc deficiency
  - Virtually identical to NME under microscope
- Biotin deficiency
  - Mimics acrodermatitis enteropathica

### Clinical

- Toxic epidermal necrolysis
  - Painful erythema with bullae and sloughing of skin
  - Full-thickness epidermal necrosis
    - In early lesions, may have individual dyskeratotic keratinocytes
  - Mild perivascular lymphocytic infiltrate
- Erythema marginatum
  - Raised, erythematous annular lesions that are transient and migratory
  - Associated with rheumatoid fever
  - Superficial perivascular infiltrate of mostly neutrophils with lymphocytes and eosinophils
  - ± vasculitis

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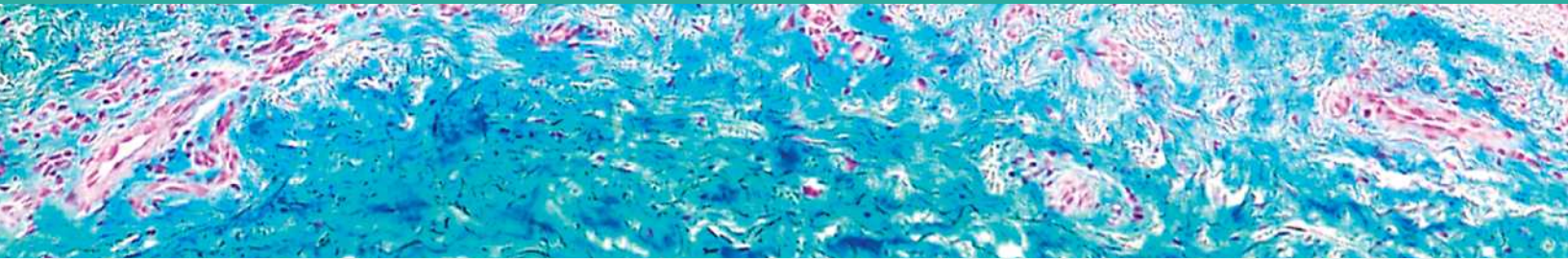
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## SECTION 9

# Mucinoses



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# Focal Cutaneous Mucinosis

## KEY FACTS

### CLINICAL ISSUES

- Site
  - Most common on face, trunk, and proximal extremities
  - May also occur in oral cavity
- Presentation
  - Asymptomatic, solitary, flesh-colored papule ~ 1.0 cm in diameter
- Treatment
  - Excision is curative
- Asymptomatic
- Rare instances of multiple papules have been reported
- Not locally aggressive; does not recur

### MICROSCOPIC

- Localized deposition of gray-blue mucin in superficial dermis
  - Mucin dissects between collagen bundles
- Fairly circumscribed without sharply delineated borders
- Paucicellular with scattered fibroblasts and small vessels

- Epithelial elements should be absent

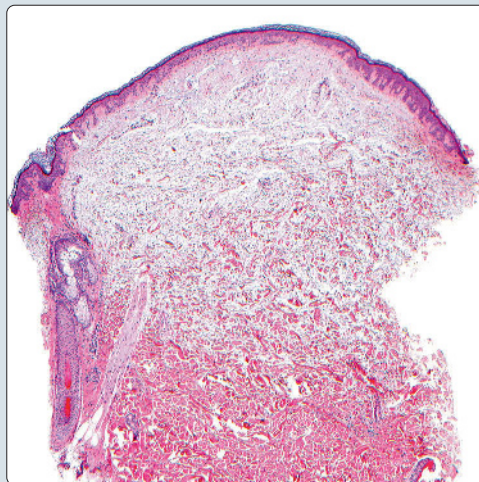
### ANCILLARY TESTS

- Alcian blue positive

### TOP DIFFERENTIAL DIAGNOSES

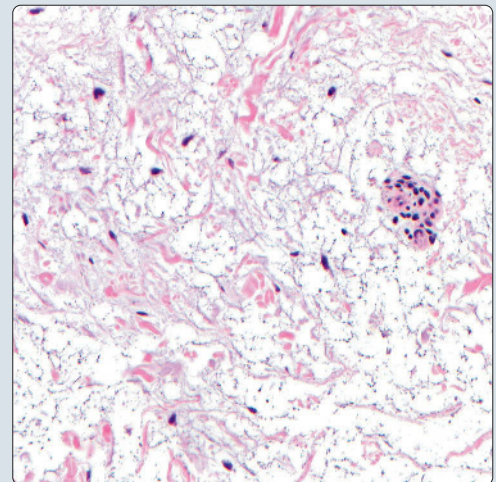
- Histopathological DDx
  - Digital mucous cyst
  - Nodular mucinosis of breast
  - Mucocele
  - Papular mucinosis (lichen myxedematosus)
  - Cutaneous myxoma
  - Mucinous (colloid) carcinoma
- Clinical DDx
  - Granuloma annulare
  - Sarcoidosis
  - Cutaneous myxoma
  - Scar
  - Lymphoma cutis

Low-Power View

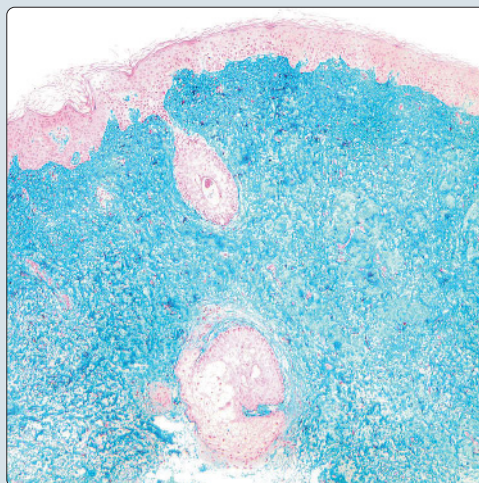


**(Left)** Focal cutaneous mucinosis is a localized collection of pale, blue-gray mucin within the superficial dermis. **(Right)** Mucin is granular and gray-blue. A few fibroblasts are present floating in the mucin. No epithelial elements should be identified.

Granular Gray-Blue Mucin

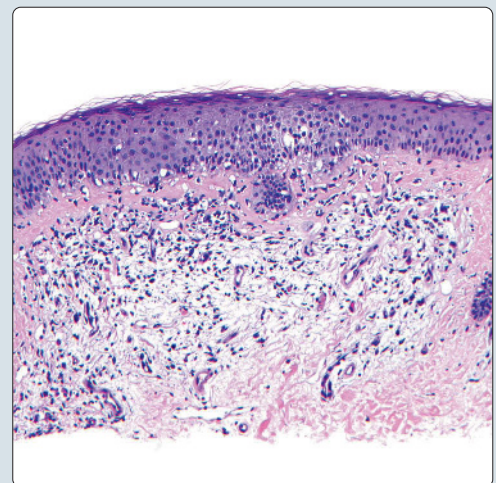


Alcian Blue



**(Left)** The mucin consists of acid mucopolysaccharides. With the use of Alcian blue, acidic mucin stains bright blue. **(Right)** Small, early lesions can appear more cellular and more vascular secondary to a decreased degree of mucin deposition.

Early Lesion





## TERMINOLOGY

### Synonyms

- Focal mucinosis

### Definitions

- Localized collection of mucin within superficial dermis
- May also occur in oral cavity

## CLINICAL ISSUES

### Epidemiology

- Has been associated with TNF- $\alpha$  antagonist therapy and thyroid dysfunction (Hashimoto thyroiditis, Graves disease)

### Site

- Most common on face, trunk, and proximal extremities
- May also occur in oral cavity

### Presentation

- Typically solitary, flesh-colored papule ~ 1.0 cm in diameter
  - Asymptomatic
- Rare instances of multiple papules have been reported

### Treatment

- Excision is curative

### Prognosis

- Not locally aggressive; does not recur

### Variants

- Oral focal mucinosis
  - Localized collections of mucin involving mandibular gingiva or palate

## MICROSCOPIC

### Histologic Features

- Localized deposition of gray-blue mucin in superficial dermis
  - Mucin consists of acidic mucopolysaccharides
- Mucin dissects between collagen bundles
  - Often significant expanses of mucin between collagen fibers
- Fairly circumscribed without sharply delineated borders
- Paucicellular with scattered fibroblasts and small vessels
- Epithelial elements should be absent

## ANCILLARY TESTS

### Histochemistry

- Alcian blue positive
  - Stains acidic mucopolysaccharides
- PAS negative
  - Stains basic mucopolysaccharides

## DIFFERENTIAL DIAGNOSIS

### Digital Mucous Cyst

- Similar to focal mucinosis but occurs on dorsum of fingers
  - Usually subungual

### Nodular Mucinosis of Breast

- Localized deposition of mucin under areola of predominantly young females
- Frequent mast cells floating within mucin

### Mucocele

- Found in areas with major or minor salivary glands (usually lip)
- Pools of acellular extravasated mucin within surrounding stroma around ruptured salivary gland or duct

### Papular Mucinosis (Lichen Myxedematosus)

- Grouped 2- to 3-mm papules of head, neck, trunk, and distal upper extremities
- Discrete form may be indistinguishable from focal cutaneous mucinosis

### Cutaneous Myxoma

- Associated with Carney complex
  - Triad of cardiac myxomas, lentigines &/or blue nevi, and endocrine overactivity
  - Autosomal dominant with mutation in *PRKAR1a* gene on chromosome 17q22-q24
- Myxoid stroma with more abundant capillaries, mast cells, fibroblasts, and interspersed small collagen fibers
- Benign epithelial elements may be present

### Mucinous (Colloid) Carcinoma

- Essentially variant of well-differentiated adenocarcinoma of multiple sites and lineages
  - e.g., breast, eccrine, and apocrine
- Clusters of low-grade malignant epithelial cells floating in large pools and lakes of mucin

### Clinical Differential Diagnosis

- Granuloma annulare
  - Circular shape
  - Clearing in center
  - Dull red color
- Sarcoidosis
  - Apple jelly color
  - Biopsy necessary to differentiate
- Cutaneous myxoma
  - Biopsy necessary to differentiate
- Scar
  - More pigment changes (pink or white)
  - History of trauma
- Lymphoma cutis
  - Pink to red discoloration
  - Biopsy necessary to differentiate

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# Myxedema

## KEY FACTS

### TERMINOLOGY

- Deposition of mucin in skin and subcutaneous tissue in patients with thyroid disease

### ETIOLOGY/PATHOGENESIS

- General myxedema: Hypothyroidism
- Pretibial myxedema: Treated hyperthyroidism (most commonly Graves disease)

### CLINICAL ISSUES

- Generalized myxedema
  - Puffy facies and nonpitting edema of hands
- Pretibial myxedema
  - Peau d'orange, nonpitting, asymptomatic edema from below knees to over dorsal feet

### MICROSCOPIC

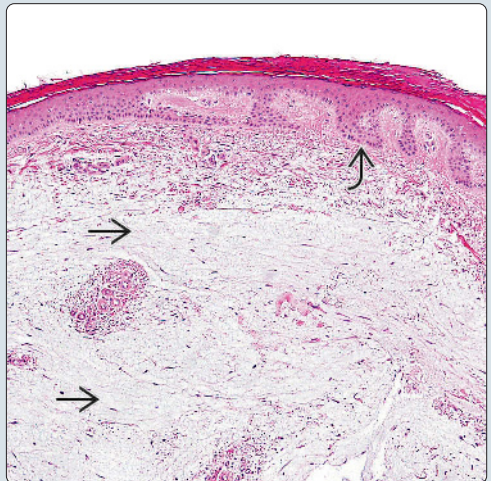
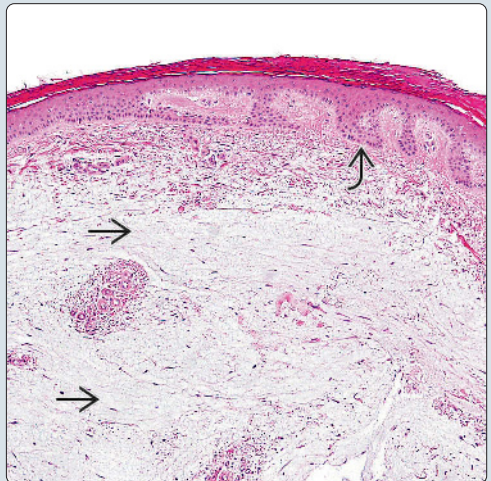
- Generalized myxedema

- Often minimal changes histologically with minimal to small amount of mucin deposits between collagen bundles in dermis
- Pretibial myxedema
  - Diffuse dermal mucin deposition in superficial and deep dermis causing separation of collagen fibers

### TOP DIFFERENTIAL DIAGNOSES

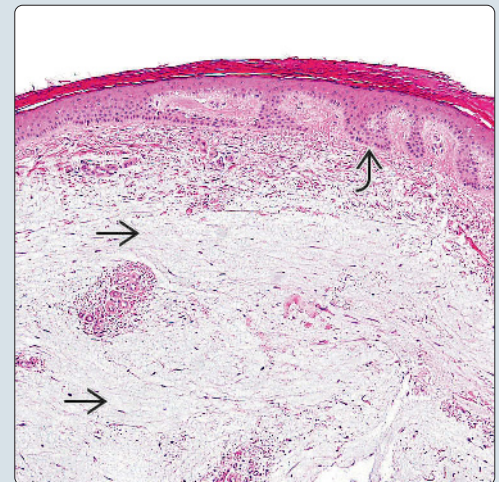
- Obesity-associated lymphedematous mucinosis
- Superficial angiomyxoma (cutaneous myxoma)
- Other cutaneous mucinoses
  - Focal cutaneous mucinosis
  - Scleromyxedema
  - Reticular erythematous mucinosis
  - Scleredema
  - Follicular mucinosis (primary or secondary)

**Infiltrated Plaque on Lower Leg**

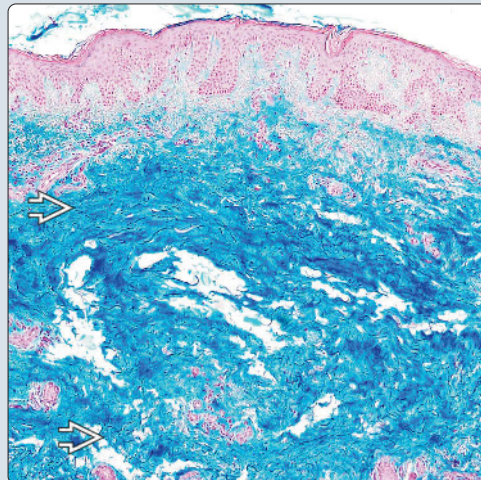
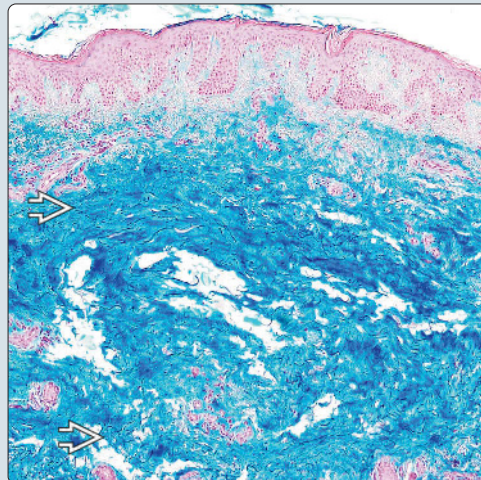
(Left) This photograph shows the lower leg of a patient with peau d'orange and a large tumor near the ankle, indicative of mucopolysaccharide deposition in pretibial myxedema. (Right) Biopsy specimen of pretibial myxedema (PM) shows diffuse mucin deposition in the reticular dermis . Note also hyperkeratosis and acanthosis . (Courtesy S. Florell, MD.)

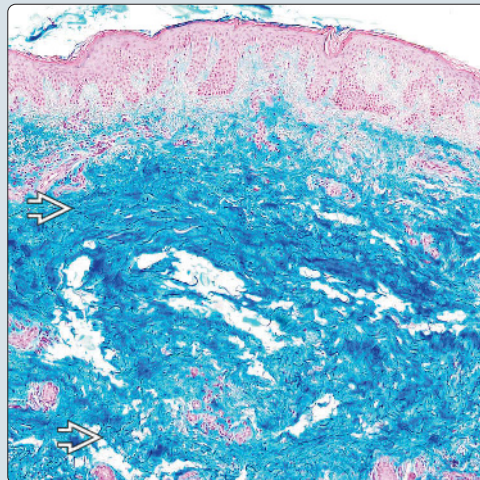


**Diffuse Mucin Deposition**

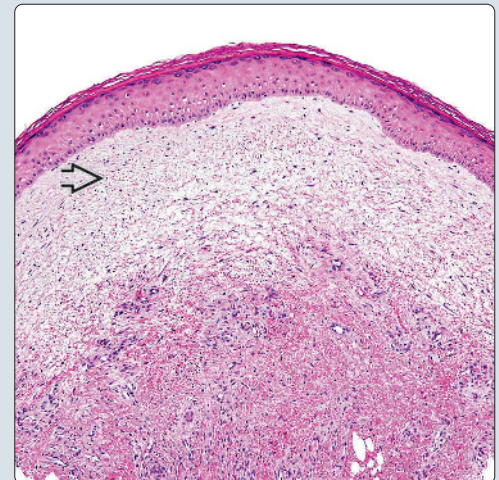


**Mucin Deposition on Hale Colloidal Iron**

(Left) Hale colloidal iron in PM demonstrates significant mucin deposition in the dermis  causing the edema. (Courtesy S. Florell, MD.) (Right) When stasis dermatitis is present in PM, the edema  is typically localized to the papillary dermis. With appropriate history, this would also be consistent with obesity-associated lymphedematous mucinosis. (Courtesy S. Florell, MD.)



**Stasis Dermatitis and Mucin in Papillary Dermis**



## TERMINOLOGY

### Definitions

- Deposition of mucin in skin and subcutaneous tissue in patients with thyroid disease

## ETIOLOGY/PATHOGENESIS

### Generalized Myxedema

- Hypothyroidism

### Pretibial Myxedema

- Unknown; may occur in Graves disease, Hashimoto thyroiditis, primary hypothyroidism, or euthyroid patients

## CLINICAL ISSUES

### Presentation

- Both entities are quite rare
- Generalized myxedema
  - Puffy facies (macroglossia, lip, periorbital infiltration, and broad nose) and nonpitting edema of hands
    - Cutis verticis gyrata may occur
    - Diffuse scalp hair loss and loss of outer 1/3 of eyebrows
- Pretibial myxedema
  - Peau d'orange, nonpitting, asymptomatic edema from below knees to over dorsal feet
    - Plaques, nodules, or tumors may form
  - Ophthalmopathy (including exophthalmos) usually present, and acropachy may be present

### Treatment

- Pretibial myxedema
  - Intralesional triamcinolone

### Prognosis

- Generalized myxedema stops progressing with thyroid therapy

## MICROSCOPIC

### Histologic Features

- Generalized myxedema
  - Often minimal changes histologically with minimal to small amount of mucin deposits between collagen bundles in dermis
    - Mucin stains, such as Hale colloidal iron, Alcian blue, or toluidine blue, can be used to highlight
- Pretibial myxedema
  - Diffuse dermal mucin deposition in superficial and deep reticular dermis
    - Causing separation of collagen fibers
  - Hyperkeratosis and acanthosis in clinically verrucous lesions
  - Fibroblasts typically not increased in number
  - Chronic lesions can show increased collagen deposition

## ANCILLARY TESTS

### Special Stains

- Hale colloidal iron, Alcian blue, or toluidine blue stain can be helpful to demonstrate mucin deposition

## DIFFERENTIAL DIAGNOSIS

### DDx of Generalized Myxedema

- Other mucinoses (discussed below)
  - Will not have clinical history of hypothyroidism
- Other minimal change or nil dermatoses
  - Clinical history, mucin stain most helpful in differentiating

### DDx of Pretibial Myxedema

- Obesity-associated lymphedematous mucinosis
  - History of obesity, but no history of thyroid disease
  - Superficial mucin overlying stasis dermatitis and lymphedema
- Superficial angiomyxoma (myxoma)
  - Associated with Carney complex if multiple
  - Thin-walled, enlarged blood vessels among nodules of mucin deposition that often extend to subcutis
  - Typically on head and neck
- Other mucinoses
  - History of treated hyperthyroidism (most commonly Graves) and significant mucin deposition in dermis of lesion from anterior lower legs favors pretibial myxedema
  - Focal cutaneous mucinosis
    - Can occur almost anywhere on body as skin-colored papule typically < 1 cm
    - Somewhat well-demarcated circular or dome-shaped nodule of mucin with intermixed spindled fibroblasts situated in dermis histologically
  - Scleromyxedema
    - Triad of increased irregular fibroblast proliferation, diffuse mucin deposition, and increased collagen
    - Classic history of 2- to 4-mm papules and plaques often on forearms, hands, face, and neck that coalesce over time to produce generalized skin thickening and folds, often involving almost entire body
  - Reticular erythematous mucinosis
    - Diffuse interstitial mucin deposition with superficial perivascular lymphocytic infiltrate (mostly T cells)
    - Typically affects young to middle-aged females on back or chest as macules, papules, or rarely plaques
  - Scleredema
    - Nonpitting induration that typically affects upper extremities with sparing of hands and feet
    - Associated with diabetes mainly but also monoclonal gammopathy and strep infection
    - Diffuse interstitial mucin deposition that splays collagen bundles, thickened reticular dermis, and normal fibroblast number
  - Follicular mucinosis (FM) (primary or secondary)
    - Mucin deposition within multiple hair follicles causing separation of cells

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# Papular Mucinosis

## KEY FACTS

### TERMINOLOGY

- Deposition of mucin amid collections of fibroblasts in multiple organs, especially skin
- Scleromyxedema is similar but also has progressive skin thickening that can involve entire body or spontaneously resolve




### MICROSCOPIC

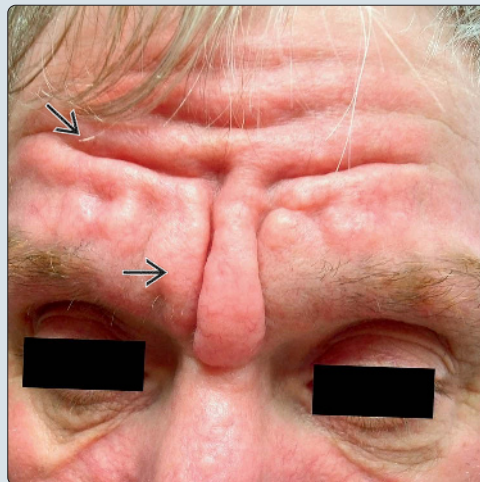
- Scleromyxedema
  - Mucin deposition, increased collagen, and increased often irregular fibroblasts in upper and mid dermis
  - Older lesions may show flattened epidermis with atrophy of pilosebaceous units and mild superficial lymphocytic perivascular infiltrate
- Lichen myxedematosus
  - Diffuse or focal mucin deposition in upper dermis with less impressive fibroblast proliferation
  - No associated skin thickening as in scleromyxedema
  - Increased collagen deposition (fibrosis) is typically absent

### TOP DIFFERENTIAL DIAGNOSES

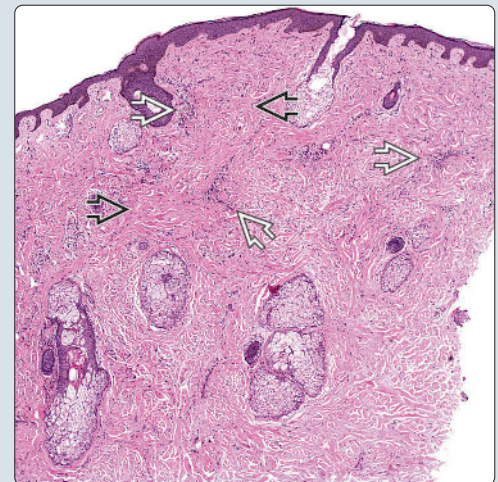
- Pretibial myxedema
  - Characteristic location over anterior lower legs
  - Fibroblasts and collagen not increased
- Nephrogenic systemic fibrosis
  - Can appear very similar to scleromyxedema, but often deeper involvement (to subcutis) in nephrogenic systemic fibrosis
  - History of gadolinium exposure and renal failure
- Scleredema
  - Nonpitting induration most common over back or chest of middle-aged diabetic women
  - No increase in fibroblasts, and degree of mucin deposition typically less than papular mucinoses
- Interstitial granuloma annulare
  - Typically has characteristic granulomatous inflammation surrounded by interstitial mucin
  - No progressive generalized involvement clinically

### Indurated Furrows



**(Left)** Scleromyxedema manifests as indurated furrows  of the forehead leading to a leonine facies in this patient who also had involvement of the trunk. Lesions had been present for over 5 years. **(Right)** Low-power view of scleromyxedema demonstrates fibrosis , increased fibroblastic proliferations , and mucin (not easily seen at this power) in the upper and mid dermis.



### Fibrosis, Fibroblasts, and Mucin

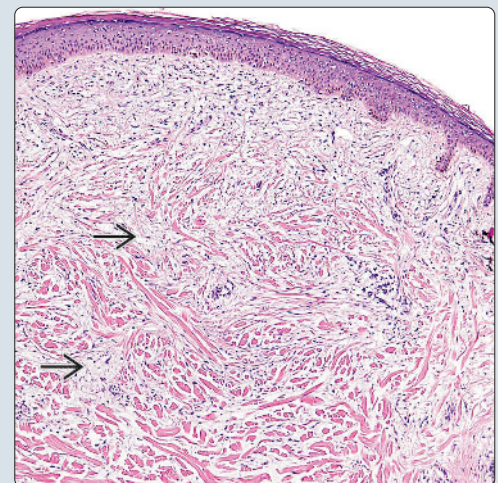


### Lichenoid Papules

**(Left)** Clinically lichen myxedematosus (LM) presents as more lichenoid papules . The back was the only area involved in this patient, so it was more consistent with LM than scleromyxedema. **(Right)** LM with mucin deposition  in the upper and mid dermis causes separation of collagen fibers and no associated fibroblast proliferation or fibrosis. (Courtesy A. Bowen, MD.)



### Mucin Deposition



## TERMINOLOGY

### Synonyms

- Scleromyxedema, lichen myxedematosus (LM)
  - All 3 terms often used interchangeably in literature
  - Clinical spectrum from LM (less skin involvement, more localized) to scleromyxedema (more severe, more diffuse skin involvement)

### Definitions

- Deposition of mucin amid collections of fibroblasts in multiple organs, especially skin
- Scleromyxedema has progressive skin thickening that can involve entire body (rarely spontaneously resolves)

## ETIOLOGY/PATHOGENESIS

### Unknown

- However, often associated with plasma cell dyscrasias, most notably monoclonal band of IgG

## CLINICAL ISSUES

### Presentation

- Presents in 3 major forms
  - Generalized papular and sclerodermoid (scleromyxedema)
    - Indurated, thickened, flesh-colored, mildly pruritic, pebbled skin over extremities, face, and trunk with marked disfigurement (leonine facies) that may begin with papules but slowly involves most of skin
    - Decreased mobility of face, fingers, and extremities ensues over years
    - Other symptoms include dysphagia, Raynaud disease, restrictive lung disease, myopathy, and neurologic defects
    - Spontaneous resolution has been reported
  - Localized (lichen myxedematosus)
    - Multiple waxy papules on face, trunk, neck, and hands without progressive involvement of other areas or progressive skin sclerosis
  - Atypical
    - Patients that have overlapping features of localized LM and scleromyxedema

### Treatment

- No proven effective therapy, but extracorporeal photophoresis has shown promise
- Other attempted treatments include systemic retinoids, electron beam, CO<sub>2</sub> laser, dermabrasion, plasmapheresis, orthovoltage radiation, thalidomide, and PUVA

### Prognosis

- Poor prognosis if associated multiple myeloma, cardiac or pulmonary involvement (generalized form)
- Good prognosis for LM

## MICROSCOPIC

### Histologic Features

- Scleromyxedema
  - Mucin deposition, increased collagen, and increased irregular fibroblasts in upper and mid dermis

- Older lesions may show flattened epidermis with atrophy of pilosebaceous units and mild superficial lymphocytic perivascular infiltrate
- LM
  - Diffuse or focal mucin deposition in upper dermis with less impressive fibroblast proliferation
  - No associated skin thickening as in scleromyxedema
  - Increased collagen deposition (fibrosis) is typically absent

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Pretibial myxedema
  - Characteristic location over anterior lower legs
  - Fibroblasts and collagen not increased
  - Clinical history of hypothyroidism
- Nephrogenic systemic fibrosis (NSF)
  - Can appear very similar to scleromyxedema, but often deeper involvement (to subcutis) in NSF
  - History of gadolinium exposure and renal failure
  - Incidence is decreasing significantly with increased knowledge of condition
- Scleredema
  - Nonpitting induration most common over back or chest of middle-aged diabetic women
  - Skin immovable and firm without color changes
  - No increase in fibroblasts, and degree of mucin deposition typically less than papular mucinosis
  - Swollen, separated collagen fibers that often extend to subcutis
- Interstitial granuloma annulare
  - Typically has characteristic granulomatous inflammation surrounded by interstitial mucin
    - Similar pattern has been reported in scleromyxedema, so clinical history of progressive generalized involvement is important

### Clinical

- Scleroderma
  - Skin indurated, shiny, and bound down
  - Hypopigmentation with perifollicular pigment retention
  - Associated with other signs of progressive systemic sclerosis
  - Characteristic histology
    - Perivascular and diffuse lymphocytic infiltrate progressing to thickened collagen bundles (sclerosis) in mid and deep dermis
    - Resulting in atrophy and loss of adnexal structures
- Eosinophilic fasciitis
  - Peripheral eosinophilia, hypergammaglobulinemia
  - Massive thickening of subcutaneous fascia with associated lymphocytes, plasma cells, and eosinophils on biopsy

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# Scleredema

## KEY FACTS

### TERMINOLOGY

- Rare, self-limited, cutaneous mucinosis especially common in women

### CLINICAL ISSUES

- Symmetric, asymptomatic indurated skin that is difficult to move

### MICROSCOPIC


- Normal epidermis often with effacement of rete ridges
- Thickened collagen bundles in upper and lower dermis with increased spaces between them
- Interstitial mucin deposits between collagen bundles
- Multiple biopsies and multiple stains may be required to demonstrate dermal mucin

### TOP DIFFERENTIAL DIAGNOSES

- Generalized myxedema
  - No associated swelling of collagen bundles on histology
  - History of hypothyroidism

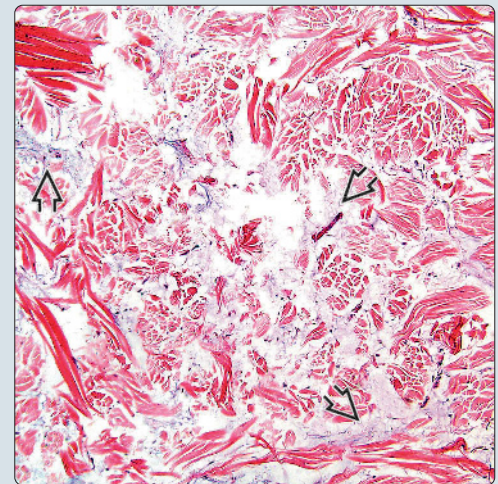
- Morphea/scleroderma
  - Chronic inflammatory infiltrate usually present at advancing edge of morphea plaques (vs. acellularity of scleredema)
- Scleromyxedema
  - Irregular fibroblast proliferation, collagen thickening, diffuse interstitial mucin deposition
  - Leonine facies (thick folds in skin that can involve entire body, do not resolve spontaneously, and respond poorly to treatment)
- Nephrogenic systemic fibrosis
  - History of gadolinium exposure, renal failure, and dialysis treatment
  - Rapid fibrosis of skin with flexion contractures
  - Often indistinguishable from scleromyxedema histologically

Light Pink Indurated Skin



**(Left)** Scleredema presented as light pink indurated skin on the back of this middle-aged diabetic woman. Firm pressure by the examiner produces only slight indentation. **(Right)** A low-power view of scleredema demonstrates separation of dermal collagen bundles with interstitial mucin deposition .

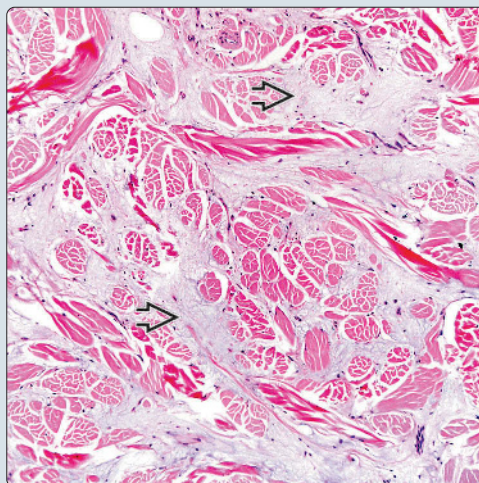


Interstitial Mucin Deposition

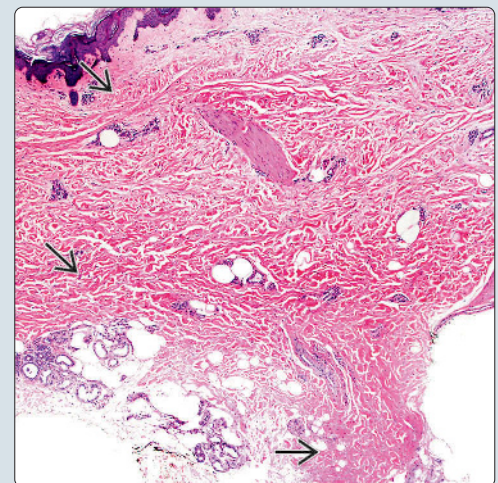


Swelled Collagen Bundles With Interstitial Mucin

**(Left)** A higher power view of scleredema shows collagen bundles that are slightly increased in size (swelling) with mucin-filled edematous spaces  between them. **(Right)** A low-power view of nephrogenic systemic fibrosis (NSF) shows haphazard thickening of collagen bundles . Increases in fibroblasts and interstitial mucin are also typically present.



Thickening of Collagen Bundles and Mucin in NSF





**TERMINOLOGY****Synonyms**

- Scleredema adultorum (however, 50% of patients may be under 20 yr old)
- Scleredema of Buschke, scleredema diabeticorum (limited to patients with diabetes)

**Definitions**

- Rare, self-limited, cutaneous mucinosis especially common in women

**ETIOLOGY/PATHOGENESIS****Unknown**

- However, associated with diabetes (usually restricted to back), acute febrile bacterial (especially strep pharyngitis) or viral illness (generalized disease), and blood dyscrasias (monoclonal gammopathy)
- Rare reports with underlying cancer, scabies, and infliximab therapy

**CLINICAL ISSUES****Epidemiology**

- Incidence
  - Very rare
- Age
  - Affects all ages
- Sex
  - M:F = 1:2

**Presentation**

- Symmetric, asymptomatic indurated skin that is difficult to move
  - May have difficulty opening mouth or wrinkling forehead
  - Usually spares hands and feet and is limited to upper body

**Treatment**

- No known effective therapy

**Prognosis**

- Usually resolves in 3-12 months (especially in diabetics)
  - Rare systemic disease with dysarthria (tongue involvement, not esophagus), involvement of skeletal muscles, viscera, pleura, ocular muscles
    - Very rarely death due to restrictive lung disease

**MICROSCOPIC****Histologic Features**

- Normal epidermis often with effacement of rete ridges
- Thickened collagen bundles in upper and lower dermis with increased spaces between them
- Interstitial mucin deposits between collagen bundles
  - Mucin deposition greatest in deeper 1/2 of dermis
  - Mucin may not be present in all lesions
    - 12 of 35 patients had no demonstrable mucin on Alcian blue staining in 1 study
  - Multiple biopsies and multiple stains may be required to demonstrate dermal mucin

**ANCILLARY TESTS****Serum Immunoglobulins**

- Can help rule out monoclonal gammopathy or hypergammaglobulinemia as cause
- Abnormalities found in 19 of 54 scleredema patients in 1 study

**Special Stains**

- Alcian blue, Toluidine blue, and H&E colloidal iron can be used to demonstrate mucin deposition
  - Mucin may not be demonstrable in all cases

**Blood Glucose, Hemoglobin A1C, or Other**

- To monitor for late-onset type 2 diabetes as cause

**DIFFERENTIAL DIAGNOSIS****Histological**

- Generalized myxedema
  - Sometimes sparse deposition of mucin similar to scleredema
  - No associated swelling of collagen bundles
  - History of hypothyroidism
- Morphea/scleroderma
  - Chronic inflammatory infiltrate usually present at advancing edge of morphea plaques (vs. acellularity of scleredema)
  - Scleroderma: Propensity for hands and feet (vs. trunk in scleredema), bound-down atrophic skin (vs. swollen puffy skin in scleredema), Raynaud phenomenon
  - Morphea: Localized form of scleroderma, large atrophic plaque with lilac pink rim with grayish-brown center progressing to porcelain white color in chronic lesions
- Scleromyxedema
  - Similar history of monoclonal gammopathy
  - Irregular fibroblast proliferation, collagen thickening, diffuse interstitial mucin deposition
  - Leonine facies (thick folds in skin that can involve entire body, do not resolve spontaneously, and respond poorly to treatment)
- Nephrogenic systemic fibrosis
  - History of gadolinium exposure, renal failure, and dialysis treatment
  - Rapid fibrosis of skin with flexion contractures
  - Often indistinguishable from scleromyxedema histologically

**SELECTED REFERENCES**

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2. Boin F et al: Scleroderma-like fibrosing disorders. *Rheum Dis Clin North Am*. 34(1):199-220; ix, 2008
3. Beers WH et al: Scleredema adultorum of Buschke: a case report and review of the literature. *Semin Arthritis Rheum*. 35(6):355-9, 2006
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# Reticular Erythematous Mucinoses

## KEY FACTS

### TERMINOLOGY

- Rare, benign mucinosis localized to skin
- Many regard reticular erythematous mucinosis (REM) as subtype of cutaneous lupus erythematosus (CLE), most closely resembling, or same entity as, tumid lupus erythematosus (TLE)
  - Progression of REM to CLE has been reported

### CLINICAL ISSUES

- Usually asymptomatic pink papules form symmetric, net-like, large plaque or sheet-like erythema
- Localized to chest or upper back, usually in middle-aged women
- Hydroxychloroquine is drug of choice
- Chronic, indolent course

### MICROSCOPIC

- Normal epidermis
- Diffuse dermal interstitial mucin deposition

- Dilated dermal vessels
- Perivascular T-cell lymphocyte-predominant perivascular infiltrate that can be mild to marked
  - Rare mast cells, histiocytes, and neutrophils may also be present

### TOP DIFFERENTIAL DIAGNOSES

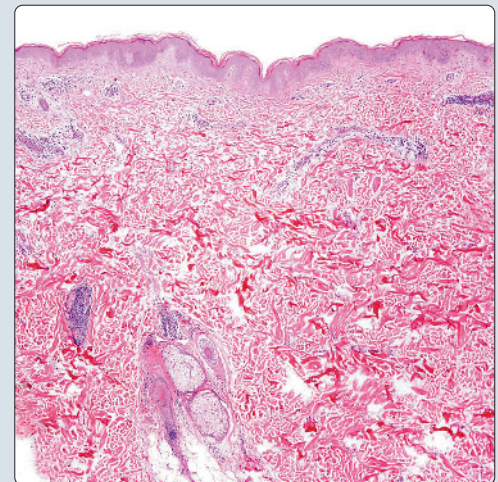
- CLE
  - Serology (ANA) typically (+) in CLE [REM and TLE (-)]
- Scleredema
  - Typically no inflammatory infiltrate
  - Characteristic thickened and separated dermal collagen fibers
- Other minimal or nil dermatoses
  - Multiple diseases can show minimal changes on biopsy
  - REM can often show minimal histologic findings
- Jessner lymphocytic infiltrate
  - May also represent form of lupus most similar to TLE
  - Typically heavier lymphocytic infiltrate

**Large Red Plaque on Breast**

(Left) This is a reticular erythematous mucinosis over the breast presenting as a large red plaque [A]. (Right) A low-power view of reticular erythematous mucinosis (REM) demonstrates a superficial and deep perivascular infiltrate with interstitial mucin deposition, which would be shown by special stains.

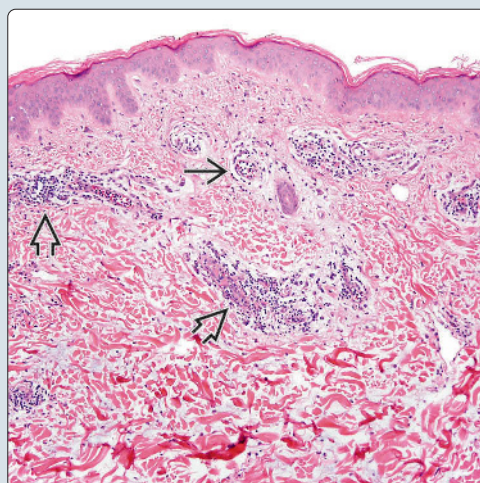


**Superficial and Deep Perivascular Infiltrate**

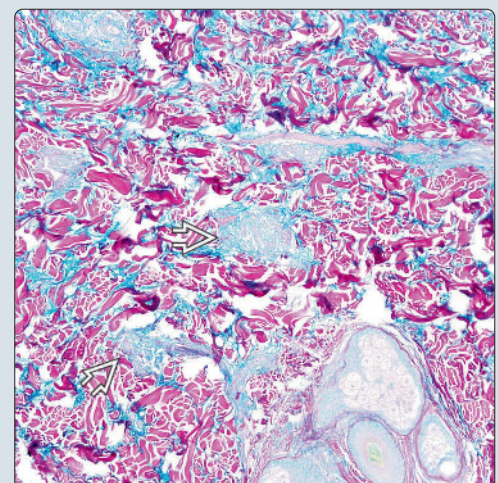


**Perivascular Lymphocyte-Predominant Infiltrate With Dilated Vessels**

(Left) A higher power view of REM demonstrates a perivascular lymphocyte-predominant infiltrate [B] with slightly dilated dermal blood vessels [C]. (Right) Hale colloidal iron stain of REM demonstrates diffuse blue staining of mucin [D] throughout the dermis. Tumid lupus erythematosus would show a similar mucin staining pattern.



**Diffuse Dermal Mucin Deposition on Colloidal Iron**



## TERMINOLOGY

### Abbreviations

- Reticular erythematous mucinosis (REM)

### Synonyms

- Midline mucinosis, plaque-like cutaneous mucinosis

### Definitions

- Rare, benign mucinosis localized to skin
- Many regard REM as subtype of cutaneous lupus erythematosus (CLE), most closely resembling or same entity as tumid lupus erythematosus (TLE)
  - Progression of REM to CLE has been reported

## ETIOLOGY/PATHOGENESIS

### Unknown

- REM may be associated or exacerbated with sun exposure
- High association with autoimmune diseases (especially thyroid) raising possibility of immune dysregulation as cause
- Possible association with smoking (10 of 11 patients in one study)

## CLINICAL ISSUES

### Site

- Localized to chest or upper back

### Presentation

- Usually in middle-aged women
  - However, can affect all ages and both sexes
- Usually asymptomatic pink papules form symmetric, net-like, large plaque or sheet-like erythema
  - Occasionally associated pruritus is reported
  - Associated telangiectasias ± 2nd concomitant disease has been reported

### Treatment

- Hydroxychloroquine is drug of choice
- Pulse dye laser, tacrolimus, pimecrolimus, sun avoidance, narrowband UVB, topical and oral corticosteroids, and other antimalarials may also help
- Author experience is that it is difficult to treat

### Prognosis

- Chronic, indolent course

## MICROSCOPIC

### Histologic Features

- Normal epidermis
- Diffuse dermal interstitial mucin deposition
- Dilated dermal vessels
- Perivascular T-cell lymphocyte-predominant infiltrate that varies from mild to marked
  - Rare mast cells, histiocytes, and neutrophils may also be present

## ANCILLARY TESTS

### Special Stains

- Hale colloidal iron, Alcian blue, or toluidine blue can be used to demonstrate interstitial deposition of mucin histologically

### Direct Immunofluorescence

- Most cases negative
- Deposition of IgM and C3 along dermal-epidermal (DE) junction has been seen in some cases

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- CLE
  - Serology (ANA) typically positive in CLE (negative in REM and TLE)
  - Can be associated with systemic disease (REM and TLE typically not)
  - Dyspigmentation following resolution of discoid lupus erythematosus lesions (not following REM or TLE)
  - Lichenoid interface dermatitis with smudging of basement membrane (absent in REM and TLE)
  - Direct immunofluorescence (DIF): Positive for IgM and C3 along DE junction in most cases (most cases of REM and TLE negative)
- Scleredema
  - Typically no inflammatory infiltrate
  - Characteristic thickened and separated dermal collagen fibers
  - Similar interstitial mucin deposition
  - More indurated clinically and usually associated with diabetes, monoclonal gammopathy, or acute viral or bacterial infection
- Other minimal or nil dermatoses
  - Multiple diseases can show minimal changes on biopsy
  - REM can often show minimal histologic findings
  - Nil dermatoses include urticaria, dermatophytosis, mastocytosis, porokeratosis, anetoderma, vitiligo, ichthyosis vulgaris, and macular amyloidosis
  - Clinical history as well as awareness of common nil dermatoses will help avoid errantly signing case out as "normal skin"
- Jessner lymphocytic infiltrate
  - Debatable whether it is discrete entity or not
  - May also represent form of lupus most similar to TLE
  - Well-demarcated erythematous plaques typically on face or neck
  - Typically heavier lymphocytic infiltrate
  - Negative DIF and interstitial mucin may be seen (just like REM)

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3. Thareja S et al: Reticular erythematous mucinosis—a review. *Int J Dermatol.* 51(8):903-9, 2012



# Digital Mucous Cyst

## KEY FACTS

### TERMINOLOGY

- Solitary, dome-shaped, skin-colored to translucent papule
- Synonyms
  - Digital myxoid cyst
  - Digital synovial cyst
  - Periungual ganglions

### ETIOLOGY/PATHOGENESIS

- Unclear etiology
- Most view digital mucous cyst and digital myxoid cyst to be synonymous

### CLINICAL ISSUES

- Relatively common lesions
- Mostly occur in adults
- Slight female predilection
- Most commonly present on dorsum of fingers
- Excellent prognosis, no malignant potential
- Treatment not necessary in most cases

- Only for symptoms such as pain, or if cosmetically bothersome

### MICROSCOPIC

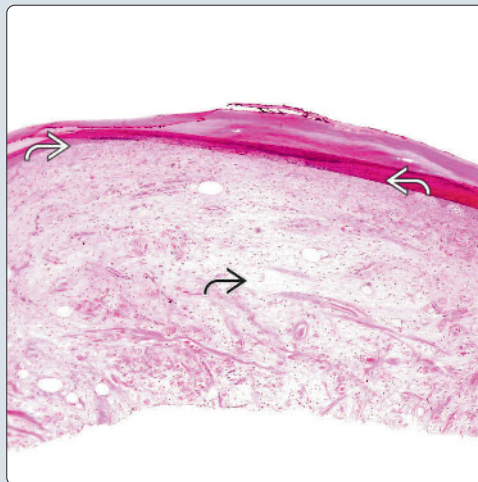
- Subepidermal cystic space or clefts with collection of mucin and stellate fibroblasts
- No epithelial lining present
- Overlying epidermis is often thinned
- Surrounding collagen is often compressed
- Often show increased numbers of small blood vessels
- Mucin is positive with colloidal iron and Alcian blue stains

### TOP DIFFERENTIAL DIAGNOSES

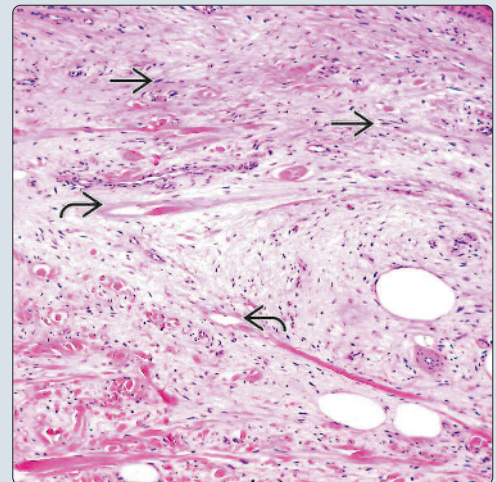
- Ganglion cyst
- Focal mucinosis
- Cutaneous myxoma (superficial angiomyxoma)

**(Left)** Earlier lesions show pools of mucin infiltrating between collagen bundles [A]. Prominent effacement of the overlying epidermal rete ridges is present [B]. **(Right)** Within the mucinous matrix, an increased number of small vessels [C] and stromal fibroblasts [D] are seen.

Low Magnification of Digital Mucus Cyst

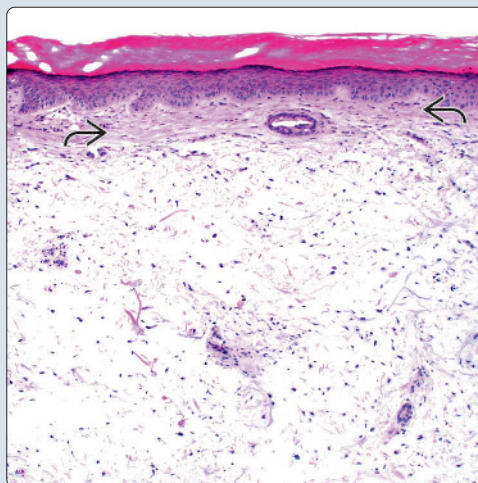


Higher Magnification of Digital Mucus Cyst

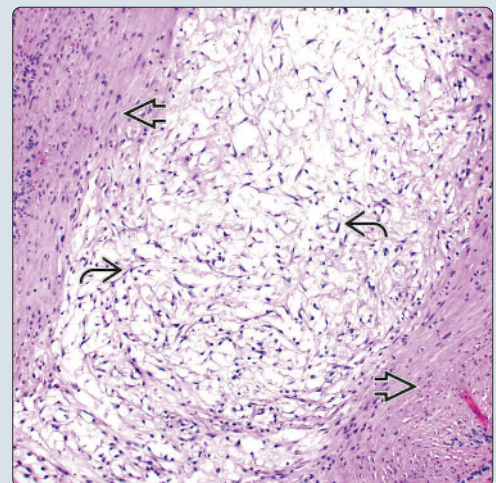


**(Left)** Digital mucous cyst at low magnification shows that the epidermis is separated from the mucinous deposits by a thin grenz zone [A]. **(Right)** Deep dermal area involved by digital mucous cyst shows a central collection of prominent mucinous material with increased numbers of small, spindle-shaped fibroblasts [B] surrounded by compressed stroma [C].

Digital Mucous Cyst With Grenz Zone



Deep Dermal Involvement



## TERMINOLOGY

### Abbreviations

- Digital mucous cyst (DMC)

### Synonyms

- Digital myxoid cyst
- Digital synovial cyst
- Nail cysts
- Periungual ganglions
- Myxomatous cutaneous cysts

### Definitions

- Solitary, dome-shaped, skin-colored to translucent papule

## ETIOLOGY/PATHOGENESIS

### Unclear Etiology

- There are 2 views as to possible etiology
  - Lesions near proximal nail may be due to local synthesis of mucin by fibroblasts
    - Identical to focal mucinosis of skin and are termed DMC
  - Lesions on distal interphalangeal joint may be due to herniation of joint lining
    - Identical to ganglion and are termed myxoid cyst
- Most view DMC and digital myxoid cyst to be synonymous

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Relatively common
- Age
  - Adults
- Sex
  - Slight female predilection
- Ethnicity
  - No ethnic predilection

### Site

- Dorsum of fingers
  - Occasionally dorsum of toes

### Presentation

- Solitary papule
- Dorsum of fingers, typically at base of nail
- Can cause deformity of involved nail

### Treatment

- Not necessary
  - Most cases are asymptomatic
- For symptoms such as pain or if cosmetically bothersome
  - Steroid injection
  - Electrocautery
  - Chemical cautery
  - Lesions tend to recur and often require multiple treatments

### Prognosis

- Excellent, no malignant potential

## MACROSCOPIC

### General Features

- Gelatinous fluid contents released during gross sectioning

### Size

- Commonly 3-7 mm

## MICROSCOPIC

### Histologic Features

- Subepidermal cystic space or clefts with collection of mucin and stellate fibroblasts
  - Overlying acral skin with stratum lucidum is diagnostic clue
- No epithelial lining present
- Overlying epidermis is often thinned
- Surrounding collagen is often compressed
- Usually show increased numbers of small blood vessels
- Mucin is strongly positive with colloidal iron and Alcian blue stains

### Cytologic Features

- Bland-appearing, small stromal fibroblasts

## DIFFERENTIAL DIAGNOSIS

### Ganglion Cyst

- DMC may be considered superficial variant of ganglion cyst
  - Ganglion cysts are larger and more deeply located; usually located around wrists

### Focal Mucinosis

- Histologically identical findings
- Location distinguishes from DMC (not on fingers)

### Cutaneous Myxoma (Superficial Angiomyxoma)

- Solitary or multiple (associated with Carney complex)
- Prominent myxoid stroma with increased numbers of fibroblasts
- Differs from DMC by increased vascularity

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Cystic space with mucin on finger is characteristic for DMC

### Pathologic Interpretation Pearls

- Subepidermal collection of mucin with stellate fibroblasts
- No epithelial lining and overlying thin acral skin with stratum lucidum

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3. Misago N et al: Digital superficial angiomyxoma. *Clin Exp Dermatol*. 32(5):536-8, 2007
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# Mucocele

## KEY FACTS

### TERMINOLOGY

- Collection of mucin within dilated space of lower lip, almost exclusively, often due to trauma or obstruction of minor salivary glands

### CLASSIFICATION

- Mucocele

### CLINICAL ISSUES

- Translucent to bluish papule on lower lip, which can sometimes leak mucin

### MICROSCOPIC


- Mucin in dilated space that lacks cell wall lining
- Granulation tissue and fibroblasts often adjacent to cystic space




### TOP DIFFERENTIAL DIAGNOSES

- Pyogenic granuloma
  - Will see well-circumscribed lobular capillary proliferation

- Papule that is often red to violaceous, with frequent ulceration and history of bleeding
- Lymphangioma
  - Dilated spaces with endothelial lining; sometimes valves can be identified
  - Papule with bluish color
  - Can drain clear fluid
  - Collapses with compression

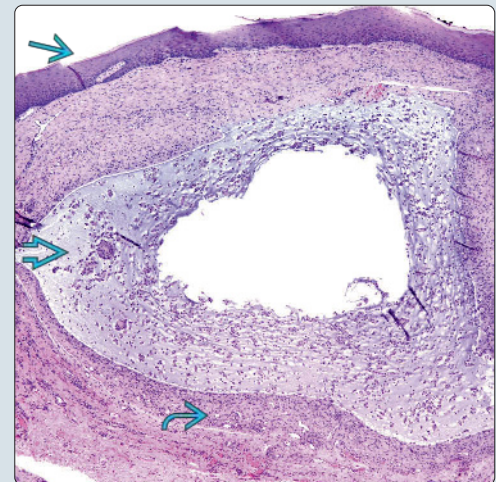
**Dome-Shaped Translucent Papule**

(Left) Mucocele of the lower lip demonstrates the dome-shaped translucent to bluish papule  often due to biting, trauma, or obstruction of the minor salivary glands. (Courtesy S. B. Woo, DMD.)



(Right) Low-power H&E demonstrates the overlying mucosal epithelium  with an underlying dilated space containing mucin . Note the predominantly lymphocytic infiltrate . (Courtesy S. Wenson, MD.)





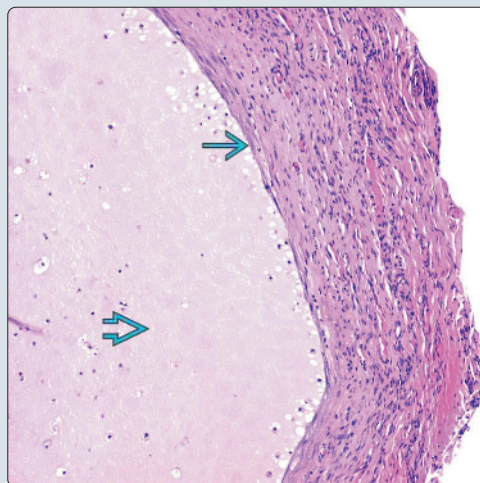
**Dilated Space Containing Mucin**



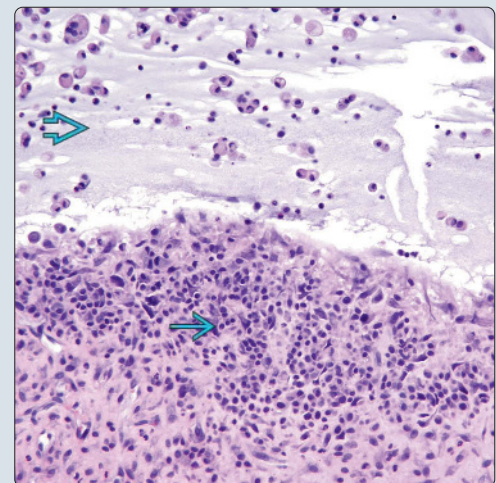
**Cystic Space With Mucin**

(Left) Medium-power H&E demonstrates the cystic space, containing mucin , which lacks a true lining . (Courtesy L. Cohen, MD.)

(Right) Higher power H&E demonstrates the cystic space, containing mucin , and the adjacent mixed inflammatory infiltrate, containing lymphocytes and fibroblasts . (Courtesy S. Wenson, MD.)



**Mucin With Adjacent Mixed Infiltrate**





## TERMINOLOGY

### Synonyms

- Mucous cyst of mouth
- Mucous retention cyst
- Mucous extravasation cyst

### Definitions

- Collection of mucin within dilated space of lower lip, almost exclusively, often due to trauma or obstruction of minor salivary glands

## CLINICAL ISSUES

### Presentation

- Dome-shaped translucent to bluish papule presenting on lower lip mucosal surface
- Ranula
  - Mucocele on floor of mouth

### Prognosis

- Surgical removal is curative

## MICROSCOPIC

### Histologic Features

- Dilated space lacking cell wall lining (not true cyst)
- Mucin a.k.a. sialomucin
- Presence of predominantly lymphocytic infiltrate
- Granulation tissue and fibroblasts often adjacent to cystic space

## ANCILLARY TESTS

### Histochemistry

- Sialomucin is PAS(+) diastase resistant

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Lymphangioma
  - Dilated spaces with endothelial lining; sometimes valves can be identified
- Pyogenic granuloma
  - Will see well-circumscribed lobular capillary proliferation

### Clinical

- Pyogenic granuloma
  - Papule that is often red to violaceous, with frequent ulceration and history of bleeding
- Lymphangioma
  - Papule with bluish color
  - Can drain clear fluid
  - Collapses with compression

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Translucent to bluish papule on lower lip, which can sometimes leak mucin

### Pathologic Interpretation Pearls

- Mucin in dilated space that lacks cell wall lining

## SELECTED REFERENCES

1. Arslan S et al: A 15-year retrospective study of 160 cases of benign lip lesions. *J Laryngol Otol.* 129(12):1224-7, 2015
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4. Paglia M et al: Mucocele of the minor salivary glands in an infant: treatment with diode laser. *Eur J Paediatr Dent.* 16(2):139-42, 2015
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## Cutaneous Myxoma

## KEY FACTS

## CLINICAL ISSUES

- Recurrences not uncommon with incomplete excision
- Carney syndrome (atrial, cutaneous, and mammary myxomas, lentigines, blue nevi, endocrine disorders, and testicular tumors)
- LAMB (lentigines, atrial myxomas, mucocutaneous myxomas, and blue nevi)
- Commonly on external auditory canal and eyelid when associated with Carney syndrome

## MACROSCOPIC

- Face, trunk, or distal extremities
- Solitary or multiple flesh-colored papule(s)

## MICROSCOPIC







- Well-circumscribed, lobular, hypocellular lesion with prominent myxoid stroma
- Bland, short, spindled to stellate cells with vesicular nuclei

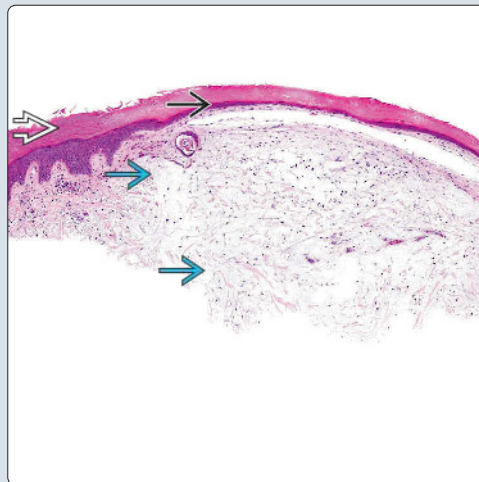
- Inflammatory infiltrate is common; presence of neutrophils differentiates myxoma from other myxoid lesions

## TOP DIFFERENTIAL DIAGNOSES

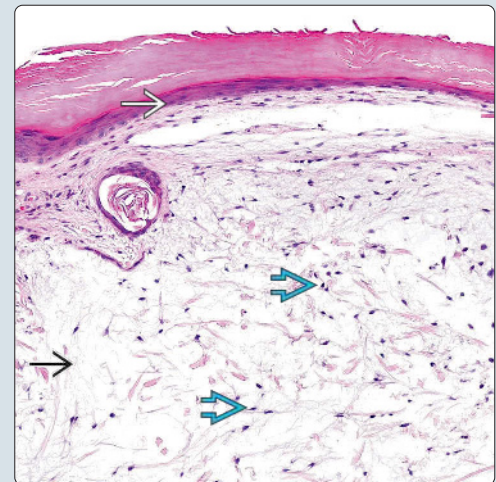
- Angiomyxoma
- Superficial acral fibromyxoma
- Digital mucous cyst
- Aggressive angiomyxoma
- Amelanotic nevus
- Dermatofibroma
- Lipoma

Accumulation of Hypocellular, Myxoid Material








(Left) Acral skin with hyperkeratosis  shows attenuation of the epidermis  overlying an accumulation of hypocellular, myxoid material . (Right) Attenuated epithelium  overlies a dermal accumulation of hypocellular myxoid material  with scattered spindled to stellate cells .

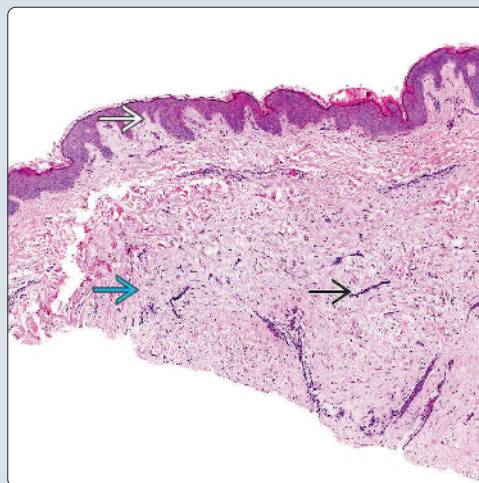


Spindled to Stellate Cells

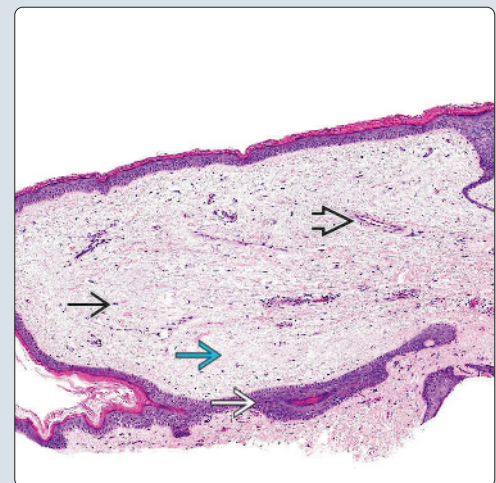


Thin Vasculature

(Left) Subtle epidermal acanthosis  overlies a hypocellular dermal lesion  with thin vasculature . (Right) Epithelial collarette  surrounds a dermal accumulation of myxoid material  admixed with scattered stellate to spindled cells  and thin vasculature .



Collarette Surrounding Myxoid Material



## TERMINOLOGY

### Synonyms

- Myxoma

## CLINICAL ISSUES

### Epidemiology

- Can be associated with various syndromes
  - Carney syndrome (atrial, cutaneous, and mammary myxomas, lentigines, blue nevi, endocrine disorders, and testicular tumors)
  - LAMB (lentigines, atrial myxomas, mucocutaneous myxomas, and blue nevi)

### Presentation

- Slow growing, flesh-colored papule(s) on head/face and distal extremities
- Commonly on external auditory canal and eyelid when associated with Carney syndrome

### Treatment

- Surgical excision is curative

### Prognosis

- Benign, slow-growing lesion with good prognosis
- Recurrences not uncommon with incomplete excision

## MACROSCOPIC

### General Features

- Face, trunk, or distal extremities
- Solitary or multiple flesh-colored papule(s)

## MICROSCOPIC

### Histologic Features

- Well-circumscribed, lobular, hypocellular lesion with prominent myxoid stroma
- Bland, short, spindled to stellate cells with vesicular nuclei
- Thin-walled vascular spaces
- Mitotic figures are rare
- Inflammatory infiltrate is common; presence of neutrophils differentiates myxoma from other myxoid lesions
- Cystically dilated follicular structures and small basaloid islands are common in cutaneous myxomas
- Histologic features similar to that of myxomas occurring elsewhere

## DIFFERENTIAL DIAGNOSIS

### Angiomyxoma

- More ill-defined lesion with more prominent thin-walled vascular channels

### Superficial Acral Fibromyxoma

- Acral location, majority involving nail bed, lacking epithelial component, higher cellularity with loose storiform to fascicular architecture set in myxoid stroma with variable vasculature

### Digital Mucous Cyst

- No epithelial cell component, mucopolysaccharide mucin that stains with Alcian blue and colloidal iron, vasculature less conspicuous

### Aggressive Angiomyxoma

- Deep lesion that can extend to subcutis, located in genital area (usually in vulva in female patients), with characteristic hyalinized vascular structures with condensation of malignant stellate cells around vessels

### Amelanotic Nevus

- Dermal or combined junctional and dermal proliferation of banal melanocytes

### Dermatofibroma

- Dermal proliferation of spindled cells in short intersecting fascicles with peripheral infiltrative growth around individual collagen bundles

### Lipoma

- Well-circumscribed dermal to subcutaneous collection of variably sized but uniformly benign lipocytes

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Prominent myxoid stroma in well-circumscribed lobular configuration within dermis
- Spindled to stellate cells without atypia
- Inflammatory infiltrate, particularly neutrophils, differentiates myxoma from other myxoid lesions

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## KEY FACTS

### TERMINOLOGY

- Alopecia mucinosa refers to primary or idiopathic follicular mucinosis
- Secondary follicular mucinosis may be observed in many disorders including cutaneous T-cell lymphoma, alopecia areata, and eosinophilic folliculitis

### ETIOLOGY/PATHOGENESIS

- Mucin is composed of hyaluronic acid and sulfated glycosaminoglycans and secreted by follicular keratinocytes

### CLINICAL ISSUES

- Alopecic plaques  $\pm$  scale, usually on head or neck

### MICROSCOPIC

- Cystic pools of mucin and lymphocytic exocytosis are present within follicular epithelium; eosinophils are common

### ANCILLARY TESTS

- CD4:CD8 ratio and T-cell receptor gene rearrangement studies do not distinguish primary follicular mucinosis from cutaneous T-cell lymphoma-associated follicular mucinosis

### TOP DIFFERENTIAL DIAGNOSES

- Folliculotropic mycosis fungoides
- Eosinophilic folliculitis
- Alopecia areata

### DIAGNOSTIC CHECKLIST

- No single histologic finding allows differentiation from mycosis fungoides
- Often secondary finding in variety of neoplastic and inflammatory conditions

Pink Plaques of Alopecia Mucinosa



*Alopecia mucinosa (primary or idiopathic follicular mucinosis) presents as pink plaques on the cheek of a child that can simulate eczema.*

## TERMINOLOGY

### Abbreviations

- Follicular mucinosis (FM)

### Synonyms

- Alopecia mucinosa
- Primary follicular mucinosis
- Idiopathic follicular mucinosis
- Secondary follicular mucinosis
- Lymphoma-associated follicular mucinosis

### Definitions

- Reactive histologic pattern, which may represent primary or secondary pathologic process

## ETIOLOGY/PATHOGENESIS

### Reactive Phenomenon

- Given variety of conditions associated with FM, production of mucin **most likely** represents reactive phenomenon
- Mucin in FM is secreted by follicular keratinocytes and is composed of hyaluronic acid and sulfated glycosaminoglycans
- Composition of follicular mucin does not vary based on associated diagnosis
- In cases of secondary FM associated with cutaneous T-cell lymphoma (CTCL), such as folliculotropic mycosis fungoides (FMF), increased expression of skin-selective homing receptors and adhesion molecules may be involved in induction of folliculotropism

## CLINICAL ISSUES

### Presentation

- 3 main clinical variants of FM
  - Benign primary or idiopathic form in children and young adults (alopecia mucinosa)
  - Benign idiopathic form in older patients but with higher risk of progression to CTCL
  - Secondary FM in adults associated with CTCL
    - Secondary FM may also be associated with nonlymphoid conditions
- Most common presentation of primary or idiopathic FM is solitary dermal plaque on head or neck, often with alopecia
  - Other presentations include follicular-based papules or acneiform lesions, scaly hairless patches or plaques, and urticarial lesions
  - Occasionally, multiple lesions with involvement of trunk or extremities may occur
- Long-term follow-up of patients < 40 years of age with primary FM demonstrated chronic persistent course but without progression to CTCL, even in patients with clonal T-cell receptor (*TCR*) rearrangement
- In children, primary FM and FM associated with CTCL are both rare and tend to run benign course with eventual resolution

### Treatment

- Drugs

- Many different treatments have been attempted for primary FM (alopecia mucinosa), most supportive evidence is anecdotal, and there is no treatment of choice
- Hydroxychloroquine is treatment with best evidence, based on small retrospective study and several reports
- Reports of successful systemic treatment with indomethacin, minocycline, isotretinoin, dapsone, and interferons have been described
- Topical treatments include pimecrolimus, tacrolimus, corticosteroids, retinoids, imiquimod, and bexarotene
- Photodynamic therapy and phototherapy with narrow band ultraviolet B or psoralen with ultraviolet A have also been used successfully

### Prognosis

- Primary or idiopathic FM tends to have chronic persistent course
- Progression to CTCL is rare

## MICROSCOPIC

### Histologic Features

- It is important to note that FM in itself is not a diagnosis but rather a reaction pattern present in wide variety of inflammatory and neoplastic conditions
- Primary or idiopathic FM is characterized by large cystic spaces within follicles filled with mucin and slight perivascular and periadnexal infiltrate of banal lymphocytes without epidermotropism
- Eosinophils are common, and follicular lymphocytic exocytosis may be prominent
- Secondary FM is present in cutaneous lupus erythematosus, folliculitis including eosinophilic folliculitis, primary spongiotic processes and lichen simplex chronicus, exaggerated insect bite reactions, leishmaniasis, alopecia areata (AA), angiolymphoid hyperplasia with eosinophilia, and polymorphous light eruption
- Associated neoplasms include folliculotropic and syringotropic mycosis fungoides, Kaposi sarcoma, nonmelanoma skin cancers, and seborrheic keratoses

## ANCILLARY TESTS

### Immunohistochemistry

- Although variable, CD4:CD8 ratio is most often equivalent (1:1) in primary FM

### Clonality Studies

- *TCR* gene rearrangement studies may detect clonality in patients with primary or idiopathic FM in up to 50% of cases
  - Does not necessarily indicate association with or progression to lymphoproliferative disorder, such as mycosis fungoides

## DIFFERENTIAL DIAGNOSIS

### Folliculotropic Mycosis Fungoides

- Histopathology
  - Most commonly reported histology demonstrates folliculocentric or folliculotropic small to medium atypical lymphocytes and FM

- Keratin-filled cysts, comedones, follicular plugging, basaloid hyperplasia, syringotropism, granulomas, and eosinophils may also be seen
- FM associated with CTCL is more likely to present with dense, band-like infiltrate with atypical lymphocytes and epidermotropism, compared to primary FM
  - However, 50% or more of FMF cases do not demonstrate epidermotropism, making this an unreliable feature
- CD4:CD8 ratio is usually  $\geq 4:1$
- TCR gene rearrangement demonstrates clonality in majority of cases
- Clinical
  - Common clinical findings include follicular papules or plaques with follicular prominence, acneiform lesions, alopecia, and cysts
  - Although most lesions are present on head and neck, patients with secondary FM associated with CTCL are more likely to have involvement of trunk or extremities than patients with primary FM
  - Lymphoma-associated FM is also more likely to be associated with multiple lesions than primary FM
- Unfortunately, no single histologic or clinical feature allows distinction of primary or idiopathic FM from secondary FM associated with mycosis fungoides
- Presence of eosinophils, deposition of mucin, epidermal exocytosis, and epidermal hyperplasia do not permit differentiation
- Evaluation of multiple clinical and histologic variables over time and clinical follow-up are necessary

## Eosinophilic Folliculitis

- Eosinophilic folliculitis has several different clinical subtypes, including classic type (Ofuji disease), infantile type, and immunosuppression-associated type, which is associated with malignancy or HIV infection
- Pruritic follicular papules, pustules, arcuate plaques, and urticarial lesions are seen
- Histology demonstrates folliculotropic infiltration of eosinophils, and secondary FM is often present
  - Spongiosis, pustulosis, and infiltration of eosinophils in adjacent sebaceous glands may also be seen
- Given overlapping histologic features with primary FM and distinctive clinical features between these entities, clinicopathologic correlation is important for differentiation

## Alopecia Areata

- May present with similar clinical findings as FM
- Secondary FM and numerous eosinophils may be seen in specimens of AA
- Characteristic histologic findings of AA, such as increased number of catagen follicles with synchronized involution, peribulbar inflammation, and miniaturization, in tandem with supportive clinical correlation, allow distinction of secondary FM in AA from primary FM

- Typically lacks dense band-like infiltrates and epidermotropism

## Pathologic Interpretation Pearls

- Often secondary finding in variety of neoplastic and inflammatory conditions
- No single histologic or clinical finding allows differentiation from mycosis fungoides

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## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

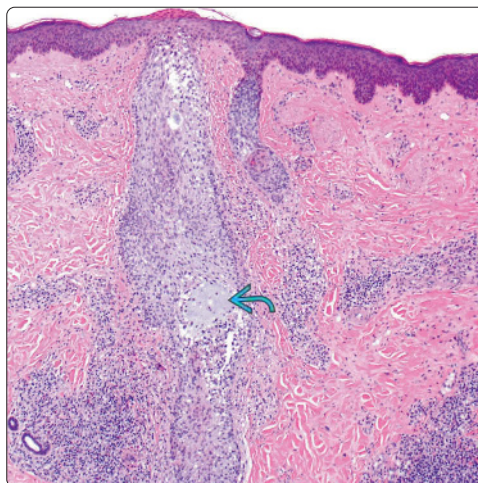
- Large cystic spaces within follicles filled with mucin
- Follicular exocytosis of banal lymphocytes
- Eosinophils are common



**Well-Demarcated, Slightly Indurated Area of Alopecia**

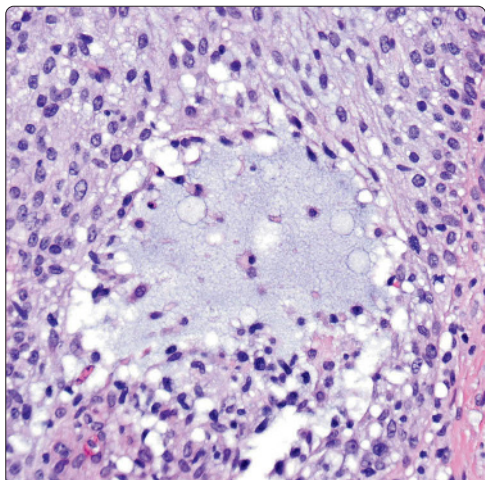


**Mucin Within Follicular Epithelium**

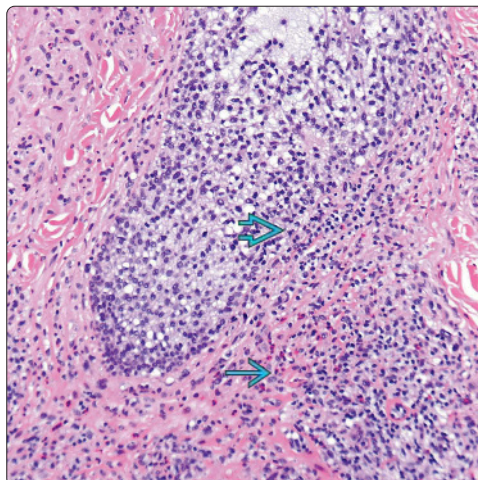


(Left) Well-demarcated, slightly indurated area of alopecia is shown on the cheek of a black man. The biopsy was compatible with alopecia mucinosa (follicular mucinosis). (Right) Low-power view of follicular mucinosis demonstrates mucin deposition and lymphocytic exocytosis within the follicular epithelium. Note the lack of interfollicular epidermal involvement.

**Pools of Mucin**

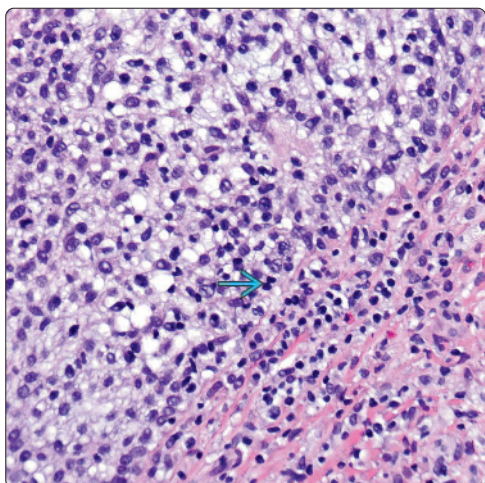


**Lymphocyte Exocytosis**

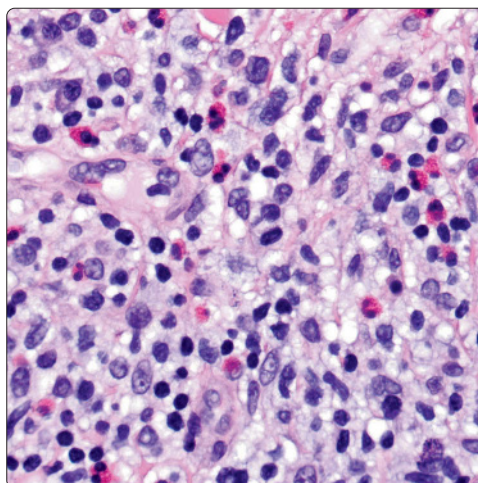


(Left) Pools of mucin can be seen within the follicular epithelium. (Right) Lymphocytic exocytosis and numerous perifollicular eosinophils are present in this biopsy specimen.

**Banal, Typical Lymphocytes**



**Numerous Eosinophils**

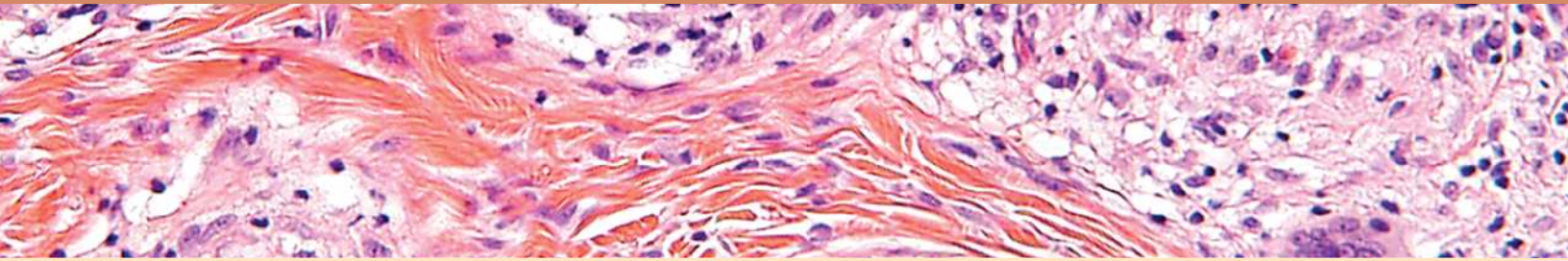


(Left) Exocytosis of numerous banal, typical lymphocytes is noted in this biopsy of follicular mucinosis. (Right) Numerous eosinophils are commonly identified, as shown on H&E stain.

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## SECTION 10

# Granulomatous Diseases



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## KEY FACTS

### TERMINOLOGY

- Chronic idiopathic granulomatous inflammation of skin, lungs, lymph nodes, heart, eyes, kidneys, and nervous system

### CLINICAL ISSUES

- 20-30% skin involvement, depending on study
- Apple jelly-colored papules, plaques, or nodules solitary or multiple
- Known to be great imitator because of heterogeneous morphologic manifestations

### MICROSCOPIC

- Noncaseating granulomas with few to no surrounding inflammatory cells ("naked granulomas") are hallmark
- Granulomas typically horizontally oriented to epidermis but can also be vertically oriented or both
- Granulomas are composed of epithelioid histiocytes and multinucleated giant cells

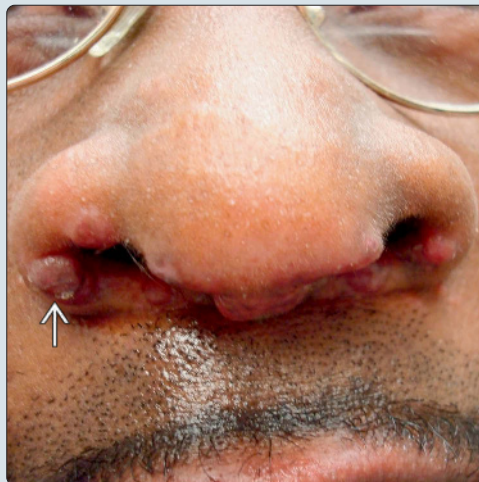
- Occasionally granulomas may be confined to subcutaneous tissue (subcutaneous or Darier-Roussy sarcoid)
- Foreign material has been reported in varying number of cases (13-77%, depending on study)

### TOP DIFFERENTIAL DIAGNOSES

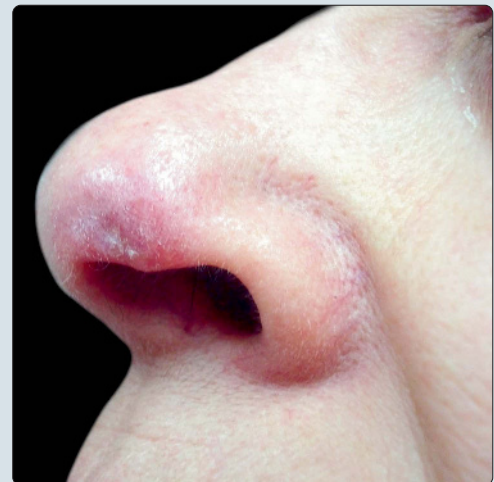
- Histologic differential diagnosis
  - Foreign body granuloma or reaction
  - Cutaneous tuberculosis
  - Tuberculoid leprosy
  - Lupus vulgaris
  - Granulomatous rosacea
  - Blau syndrome (familial juvenile systemic granulomatosis or Jabs syndrome)
- Clinical differential diagnosis
  - Granuloma annulare
  - Necrobiosis lipoidica diabeticorum

**Apple Jelly-Colored Papules**

(Left) Sarcoidosis presented as apple jelly-colored, slightly pink discrete papules on the rim of the nose of an African American man. (Right) This image shows sarcoidosis ulcerative plaque healed with a white atrophic scar on the end of the nose.

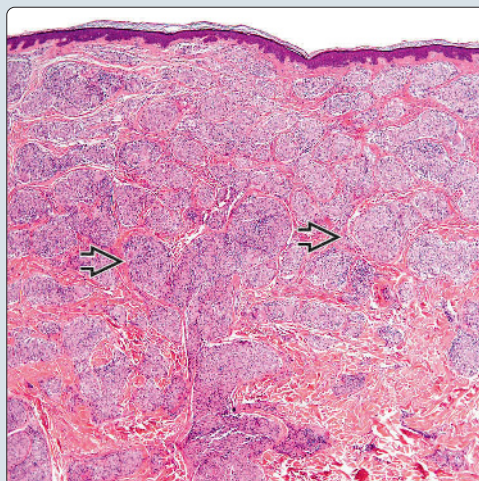


**Atrophic Scar**

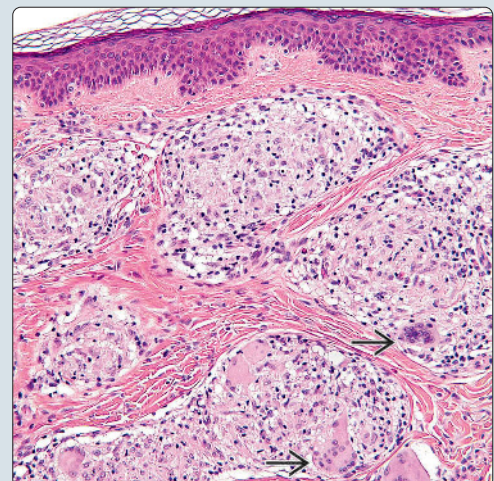


**Noncaseating Granulomas**

(Left) This is a low-power view of a sarcoid biopsy. Note the numerous naked granulomas filling the dermis. (Courtesy L. Coleman, MD.) (Right) Naked granulomas are characteristic of sarcoidosis and are composed of epithelioid histiocytes and multinucleated giant cells.



**Naked Granulomas**



**TERMINOLOGY****Synonyms**

- Boeck disease, sarcoid

**Definitions**

- Chronic idiopathic granulomatous inflammation of skin, lungs, lymph nodes, heart, eyes, kidneys, and nervous system

**ETIOLOGY/PATHOGENESIS****Environmental Exposure**

- Foreign body material is sometimes identified in biopsies of sarcoidosis, suggesting that foreign material may serve as nidus for granuloma formation
  - Exact etiology of sarcoidosis is still unknown, however

**CLINICAL ISSUES****Presentation**

- Commonly affects lungs, lymph nodes, eyes, and skin
- 20-30% skin involvement, depending on study
  - Apple jelly-colored papules, plaques, or nodules solitary or multiple
    - Known to be great imitator because of heterogeneous morphologic manifestations
  - Most common underlying disease to cause erythema nodosum (indicates chronic benign course)
  - Other forms include psoriasiform, ichthyosiform, erythrodermic, hypopigmented, erythrodermic, atrophic, ulcerative, verrucous, scar, nail, alopecia, and telangiectatic
- Subcutaneous sarcoidosis (Darier-Roussy sarcoidosis)
  - Single to multiple firm, flesh-colored deep nodules that may erupt in clusters, usually on upper extremities
- Lupus pernio
  - Chronic papulonodular eruption of violaceous, indurated papules, nodules, and plaques, primarily around central face and alae of nose

**Treatment**

- Topical, intralesional, and systemic corticosteroids are mainstay
- Methotrexate, allopurinol, hydroxychloroquine, doxycycline, and minocycline have their advocates

**Prognosis**

- Remission without sequelae in 2/3
- 1/3 have persistent disease with organ impairment
- ≤ 5% fatal

**MICROSCOPIC****Histologic Features**

- Epidermal changes present in about 1/2 of cases
  - Atrophy, parakeratosis, and acanthosis most commonly
- Noncaseating granulomas with few to no surrounding inflammatory cells ("naked granulomas") are hallmark
  - Granulomas are composed of epithelioid histiocytes and multinucleated giant cells
  - Granulomas usually surrounded by small number of CD4- and CD8-positive lymphocytes

- Granulomas typically horizontally oriented to epidermis but can also be vertically oriented or mixture of both
- Mild fibrosis rarely reported
- Depending on clinical type, granulomas may be located
  - Only in superficial papillary dermis
  - Diffusely throughout papillary and reticular dermis
  - Confined to subcutaneous tissue (subcutaneous or Darier-Roussy sarcoid)
- Rarely granulomas can have focal necrosis
  - Special stains necessary to rule out mycobacterium tuberculosis
- Foreign material has been reported in varying number of cases (13-77%, depending on study)

**Cytologic Features**

- Schaumann bodies (conchoidal bodies)
  - Refractile, concentric calcium complexes composed of calcium oxalate often found within giant cells in sarcoid
    - Not specific, as they can sometimes also be seen in tuberculous granulomas
- Asteroid bodies
  - Pink stellate inclusions often seen in multinucleated giant cells containing rays that radiate from central core
  - Also not specific for sarcoid, as they can also be seen in granulomas of foreign body reactions
- According to one study, asteroid or Schaumann bodies were seen in 32% of cases

**ANCILLARY TESTS****Histochemistry**

- Stains for acid-fast bacilli (AFB) and fungi should be performed on any biopsy specimen that demonstrates evidence of caseating or noncaseating granulomas
  - GMS and AFB stains are good options

**DIFFERENTIAL DIAGNOSIS****Histologic**

- Foreign body granuloma or reaction
  - Polarizable material may be seen
  - Foreign body material may be easily discernible
  - Solitary lesion at site of prior trauma may favor foreign body granuloma
  - **Caveat**
    - Sarcoidosis and foreign body granulomas may not be mutually exclusive, so careful clinical correlation is warranted
    - Foreign body material reportedly identified in 13-77% of cases of sarcoidosis, depending on study
- Cutaneous tuberculosis
  - Granulomas typically caseating with central necrosis
    - However, focal necrosis may rarely be present in sarcoid as well
  - Clinical history of cough, fever, and weight loss in high-risk patient (traveled to or from endemic area)
  - Ancillary tests such as
    - Tuberculin skin test, AFB culture (gold standard, most sensitive), or QuantiFERON-TB Gold in tube (for latent infection) helpful
    - AFB stain on skin biopsy has high specificity but lower sensitivity

- Tuberculoid leprosy
  - Large, annular, hypopigmented, atrophic macules with well-defined, erythematous, raised borders
  - Epithelioid granulomas typically surround neurovascular bundles on biopsy
    - Dermal nerves often swollen, damaged, or destroyed
- Lupus vulgaris
  - Postprimary, chronic, progressive form of cutaneous tuberculosis
    - Named for clinical ability to turn into disfiguring ulcers if left untreated
    - Multiple erythematous papules or nodules forming plaque or crusted ulcer (more rare)
  - History of TB infection
  - Tuberculoid granulomas are typically confluent throughout dermis
- Granulomatous rosacea
  - Distinctive papular form of rosacea found primarily on cheeks, nose, and perioral areas
  - May contain noncaseating epithelioid granulomas with multinucleated giant cells, as in sarcoid
    - Granulomas often centered on ruptured hair follicles
  - Perivascular and perifollicular lymphohistiocytic infiltrate in nonpustular lesions
  - Granulomatous inflammation and abscess formation around follicles in papulopustular granulomatous rosacea
- Blau syndrome (familial juvenile systemic granulomatosis or Jabs syndrome)
  - Autosomal dominant inherited disorder caused by mutations in *NOD2/CARD15* gene, characterized by granulomatous arthritis, iritis, and skin rash
  - Usually affects preschool age children < 4 years of age
    - Clinically indistinguishable from early-onset sarcoid
  - Ill-defined, superficial, dermal noncaseating epithelioid granulomas with occasional multinucleate giant cells and perivascular lymphomononuclear infiltrates on biopsy

## Clinical

- Granuloma annulare
  - No systemic diseases
  - Circular with central clearing, mainly over joints
  - Foci of necrobiosis surrounded by palisaded histiocytes on biopsy
- Necrobiosis lipoidica diabetorum
  - Associated with diabetes mellitus
  - Pretibial with telangiectasias and central yellow discoloration and possibly ulceration
  - Classically large areas of necrobiosis alternating with chronic inflammatory infiltrate composed of histiocytes, lymphocytes, giant cells, and plasma cells in multiple tiered layers on biopsy
- Lymphoma cutis
  - Associated with systemic lymphoma
  - More pink than yellowish
  - Dense, typically dermal lymphocytic infiltrate with clonal B- or T-cell predominance demonstrated by immunohistochemistry
    - Grenz zone typically present in B-cell cutaneous lymphomas, absent in T-cell cutaneous lymphomas
- Deep fungus
  - Often with epidermal disease such as scale, crust, ulcer, or desquamation
  - Positive culture
  - Often pseudoepitheliomatous hyperplasia or deep-seated subcutaneous abscesses on biopsy
    - Organisms can often be identified on H&E or with special stains
- Keloid
  - Presents at site of trauma (remember sarcoid can occur in scar)
  - Rock hard, elevated, and deeper pink or white
  - May be painful
  - Biopsy may actually make it grow more aggressively
  - Histology is characteristic
    - Broad, irregular, abnormally thick, and hyalinized collagen bundles ("keloidal collagen") in thickened dermis
- Hypertrophic lichen planus
  - Prefers pretibial location
  - Can occur at site of trauma (koebnerization)
  - Follicular plugs may be seen, and color is more purple
  - May be very pruritic
  - Histopathology is distinctive
    - Epidermal psoriasiform hyperplasia, streaked collagen, and lichenoid interface changes often localized to tips of rete ridges

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Sarcoidosis is largely diagnosis of exclusion
  - Only when clinical and radiologic findings have ruled out other entities and naked granulomas are seen on biopsy with no evidence of other causes (i.e., infectious organisms) can proper diagnosis be made
- Birefringent foreign body material has been observed in 13-77% of cases according to one study and does not rule out diagnosis of sarcoidosis
  - Foreign body granulomas and sarcoid may not be mutually exclusive of one another
  - Foreign material may play role in sarcoidal granuloma formation
  - Another reason clinical correlation is very important

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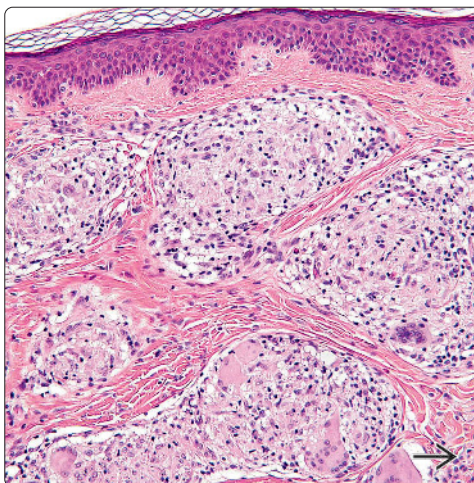
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**Hypopigmented Sarcoid**

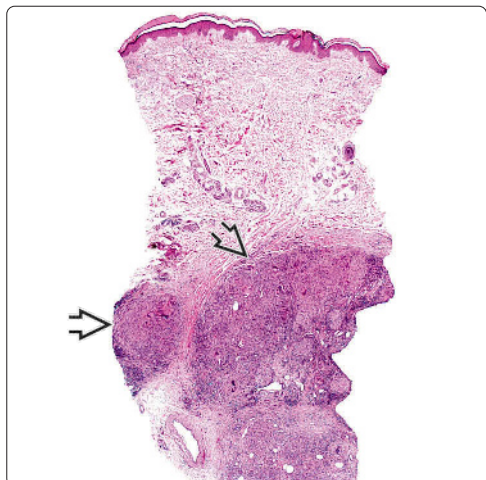


**Granulomas of Epithelioid Histiocytes and Multinucleated Giant Cells**

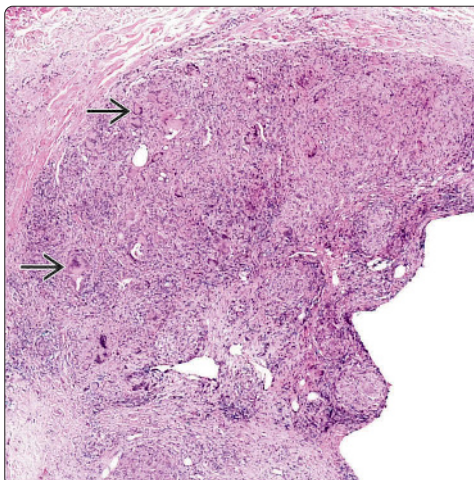


(Left) This patient presented with hypopigmented sarcoid on the side of the cheek [box] with indurated subcutaneous sarcoid on the side of the nose, causing a rosacea-like deformity. She also had pulmonary sarcoid and sarcoidal iritis. (Right) High-power view of cutaneous sarcoidosis demonstrates naked granulomas composed of epithelioid histiocytes and multinucleated giant cells [box]. (Courtesy L. Coleman, MD.)

**Darier-Roussy Sarcoid**

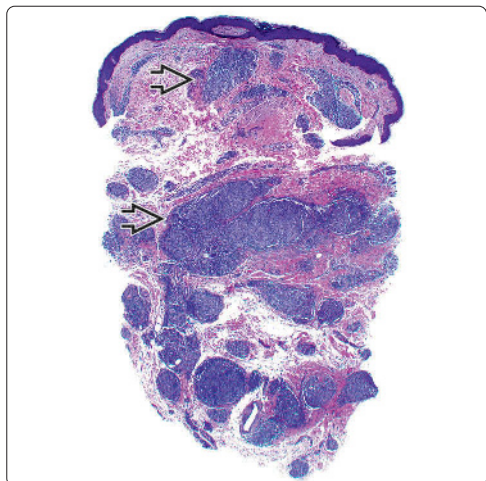


**Multinucleated Giant Cells in Subcutaneous Sarcoidosis**

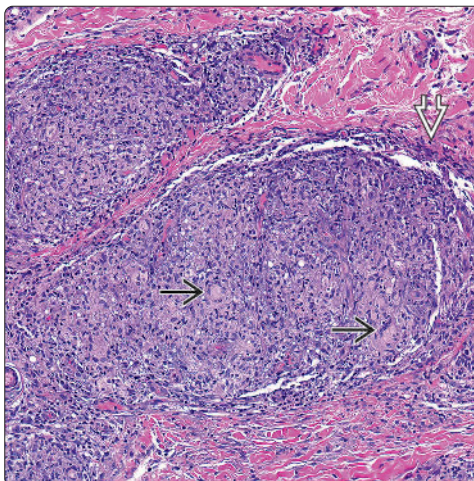


(Left) Subcutaneous sarcoidosis demonstrates large naked granulomas deep in the reticular dermis [box]. (Right) High-power view of subcutaneous sarcoidosis demonstrates epithelioid histiocytes and numerous multinucleated giant cells [box].

**Diffuse Noncaseating Granulomas**



**Epithelioid Histiocytes and Multinucleated Giant Cells**



(Left) Low-power view of sarcoidosis demonstrates discrete noncaseating naked granulomas [box] arranged horizontal to the epidermis with occasional vertical orientation. (Courtesy UCSF Dermatopathology Service.) (Right) Higher power view of the noncaseating granulomas of sarcoid demonstrates numerous epithelioid histiocytes with occasional multinucleated giant cells [box] and a very mild peripheral lymphocytic infiltrate [box]. (Courtesy UCSF Dermatopathology Service.)



## Granuloma Annulare

## KEY FACTS

## TERMINOLOGY

- Idiopathic granulomatous skin disease

## CLINICAL ISSUES

- Most commonly localized over backs of hands/feet or on arms/legs
- Pink-red to slightly brown or purple 1- to 2-mm papules in annular arrangements of 1-5 cm in diameter
- Deep or subcutaneous form
  - More common in children over pretibial surface; other common sites include hands, scalp, and buttocks
- Generalized form
  - More commonly seen in adults

## MICROSCOPIC

- Interstitial pattern
  - "Busy" dermis of interstitial histiocytes, perivascular lymphocytes
- Palisaded pattern

- Central mucin with surrounding palisade of histiocytes
- Variable numbers of giant cells and occasional presence of elastophagocytosis
- Generalized granuloma annulare
  - Palisading may be inconspicuous
  - Superficial papillary dermal granulomas

## TOP DIFFERENTIAL DIAGNOSES

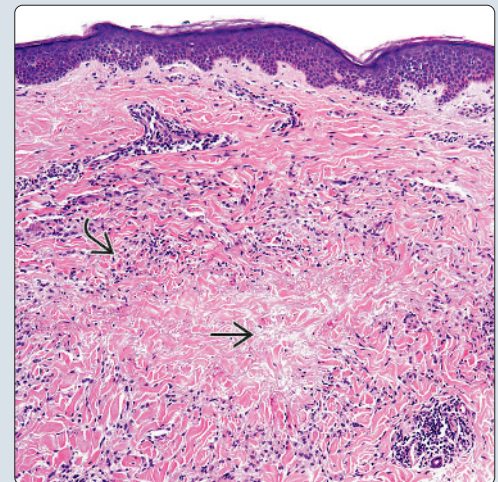
- Interstitial pattern
  - Interstitial granulomatous dermatitis
  - Interstitial mycosis fungoides
- Palisaded pattern
  - Necrobiosis lipoidica
  - Annular elastolytic giant cell granuloma
  - Rheumatoid nodule
  - Palisaded neutrophilic and granulomatous dermatitis

Annular Pink Papules

(Left) This photograph of granuloma annulare shows annular arrangements of pink papules on the dorsal hand. There is no surface scale. (Courtesy Yale Residents' Collection.) (Right) Granuloma annulare typically shows a palisade of histiocytes around central mucin. There is a perivascular lymphocytic infiltrate.

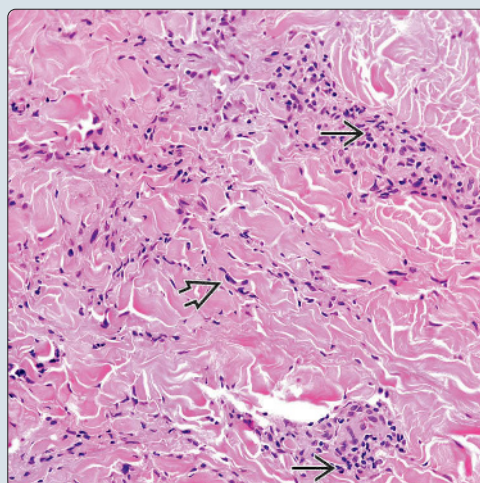


Palisading Histiocytes Around Mucin

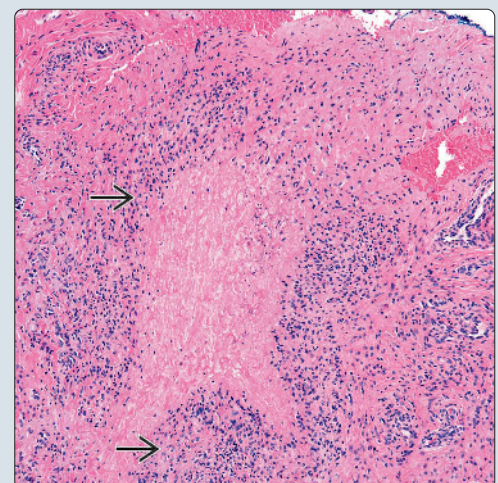


Interstitial Variant

(Left) In the interstitial type of granuloma annulare, there are histiocytes infiltrating between collagen bundles. There is a perivascular lymphocytic infiltrate. (Right) In this example of deep granuloma annulare in the subcutaneous tissue, there is palisading of histiocytes around central mucin.



Deep Granuloma Annulare



**TERMINOLOGY****Abbreviations**

- Granuloma annulare (GA)

**Synonyms**

- Deep GA = pseudorheumatoid nodule

**Definitions**

- Idiopathic granulomatous skin disease

**CLINICAL ISSUES****Epidemiology**

- Age
  - More common in children/young adults
- Sex
  - More common in female patients

**Site**

- Most commonly over backs of hands/feet or on arms/legs

**Presentation**

- Most common form: Localized
  - Pink-red to slightly brown or purple 1- to 2-mm papules in annular arrangements of 1-5 cm in diameter
  - No scale
  - Generally asymptomatic
- Subtypes
  - Deep or subcutaneous: More common in children over pretibial surface; other common sites include hands, scalp, and buttocks
  - Perforating: Umbilicated papules
  - Generalized: More commonly seen in adults
    - May be associated with diabetes mellitus or HIV infection
    - Extensive involvement of skin surface that may be composed of annular arrangements of papules (like most common form of GA) **or** pink-red papules without annular configuration

**Treatment**

- Optional
  - Intralesional or topical corticosteroids most commonly used

**Prognosis**

- Most common form may resolve spontaneously over several years

**MICROSCOPIC****Histologic Features**

- Interstitial pattern
  - "Busy" dermis
  - Interstitial histiocytes, perivascular lymphocytes
- Palisaded pattern
  - Central mucin with surrounding palisade of histiocytes
    - Neutrophils &/or neutrophilic dust sometimes present
    - Mitoses may be evident in histiocytes
    - Variable numbers of giant cells and occasional presence of elastophagocytosis
    - Rarely, small vessel vasculitis evident

- Perivascular lymphocytes and sometimes eosinophils
- Other
  - Sarcoidal pattern of GA is uncommon: Has increased mucin by report
  - Generalized GA
    - Palisading may be inconspicuous
    - Superficial papillary dermal granulomas

**DIFFERENTIAL DIAGNOSIS****Interstitial Pattern**

- Interstitial granulomatous dermatitis
  - Clinical
    - Various presentations described, but commonly ill-defined, faint pink patches on trunk
  - Histopathologic
    - Varying histopathology in literature, but commonly interstitial infiltrate of histiocytes, neutrophils/eosinophils; vacuolar change may be evident
- Interstitial mycosis fungoides
  - Clinical
    - Patient generally has preceding diagnosis of mycosis fungoides
  - Histopathologic
    - Interstitial infiltrate of lymphocytes

**Palisaded Pattern**

- Necrobiosis lipoidica
  - Clinical
    - Typically orange-pink atrophic patch on shin
  - Histopathologic
    - Layers of altered collagen; mucin not prominent; plasma cells and giant cells; may extend to subcutaneous
- Annular elastolytic giant cell granuloma
  - Clinical
    - Sharply demarcated annular lesions that tend to be in sun-exposed areas
  - Histopathologic
    - Trizonal: Absent elastic fibers bordered by giant cells with elastophagocytosis and outer zone of retained elastic fibers
- Rheumatoid nodule
  - Clinical
    - Subcutaneous/dermal nodule, most commonly in patients with rheumatoid arthritis
  - Histopathologic
    - Palisading histiocytes around central red fibrin
- Palisaded neutrophilic and granulomatous dermatitis
  - Clinical
    - Commonly papules on elbows, may show umbilication
  - Histopathologic
    - Palisade of histiocytes around central area with variable necrosis and neutrophils

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## KEY FACTS

### CLINICAL ISSUES

- More common in adults, but described in children
- Most often pretibial
  - Bilateral or unilateral
- Initially red-pink macule/papule, enlarges slowly over time
- Center becomes atrophic and orange-yellow-brown with telangiectasias
- Border may be raised or violaceous
- Associated with diabetes mellitus (may be presenting sign)
  - Consider fasting glucose
- Lesions evolve over several years then tend to stabilize

### MICROSCOPIC

- Generally centered in lower dermis
- Well-developed lesions show layers of altered collagen (necrobiosis) alternating with layers of inflammation
- Inflammatory infiltrate includes giant cells, plasma cells, histiocytes, lymphocytes

- Epithelioid granulomas (may predominate in occasional cases) or cholesterol clefts may be present

### TOP DIFFERENTIAL DIAGNOSES

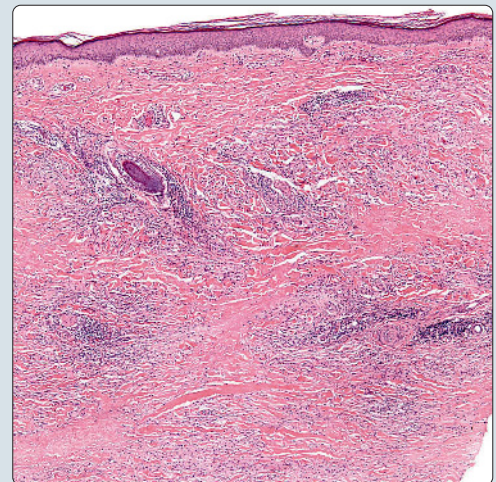
- Granuloma annulare
  - Areas of altered collagen tend to be encircled by palisading histiocytes
  - Altered collagen interspersed with mucin
  - Tends to be centered in dermis
- Necrobiotic xanthogranuloma
  - Tend to be periorbital, but various sites can be affected
  - Irregular areas of altered collagen
  - Interspersed inflammation
  - Often includes unusual giant cells
- Rheumatoid nodule
  - Palisades of histiocytes surrounding central fibrin
- Sarcoidosis
  - Classically epithelioid granulomas without palisading

**Plaques on Bilateral Shins With Central Atrophy**

(Left) In this case, lesions of necrobiosis lipoidica affect the bilateral shins. A larger plaque on the right shin has central atrophy. (Courtesy Yale Residents' Collection.) (Right) Necrobiosis lipoidica shows layers of altered collagen sandwiched between inflammatory cells. There is a perivascular lymphocytic infiltrate.

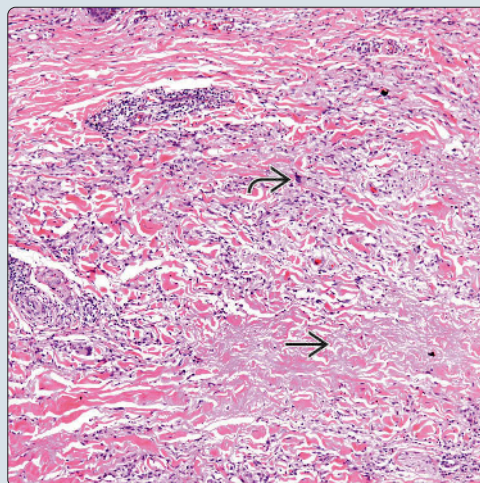


**Layers of Altered Collagen Sandwiched Between Inflammation**

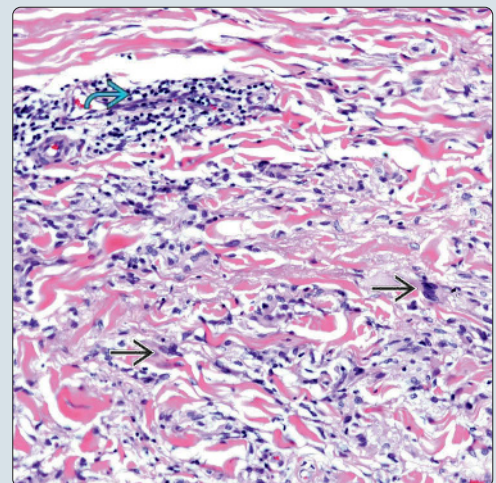


**Altered Collagen With Surrounding Inflammation**

(Left) In necrobiosis lipoidica, there is altered collagen [red box] surrounded by inflammatory cells. Giant cells are evident [blue box]. (Right) The inflammatory infiltrate in necrobiosis lipoidica consists of histiocytes, giant cells [red box], lymphocytes, and plasma cells sandwiched between layers of altered collagen. There is a perivascular lymphocytic infiltrate [blue box].



**Lymphocytes, Histiocytes, Giant Cells, and Plasma Cells**



**TERMINOLOGY****Synonyms**

- Necrobiosis lipoidica diabetorum (NLD)

**ETIOLOGY/PATHOGENESIS****Systemic Disease Association**

- Diabetes mellitus
  - Uncommon among diabetics (< 1%)
    - In diabetics, NLD is risk factor for retinopathy &/or nephropathy
  - In patients with NLD, minority have existing diabetes mellitus and ~ 10% will develop diabetes mellitus
  - Family history of diabetes mellitus may be present
- Rheumatoid arthritis, sarcoid, thyrotoxicosis, and inflammatory bowel disease are rarer associations

**Unknown**

- Diabetic vasculopathy has been proposed

**CLINICAL ISSUES****Epidemiology**

- Age
  - More common in adults, but described in children

**Site**

- Most often pretibial
- Unusual sites have been reported (e.g., genital)

**Presentation**

- Bilateral or unilateral
- Initially red-pink macule/papule (several mm)
- Enlarges slowly over time
- Center becomes atrophic and orange-yellow-brown with telangiectasias and porcelain sheen
- Border may be violaceous
- Lesions can ulcerate
- Can occasionally present with papules &/or nodules

**Laboratory Tests**

- Associated with diabetes mellitus (may be presenting sign)
  - Consider fasting glucose

**Treatment**

- Options, risks, complications
  - If asymptomatic, treatment not necessary
  - Rarely, lesions spontaneously resolve
- Drugs
  - Intralesional or topical corticosteroids
  - Topical calcineurin inhibitors
  - Light therapy
  - Severe cases (e.g., with ulceration) may need systemic treatments
    - Oral immunosuppressants like methotrexate
    - Plaquenil
    - TNF- $\alpha$  inhibitors

**Prognosis**

- Lesions evolve over several years then tend to stabilize

**MICROSCOPIC****Histologic Features**

- Generally centered in lower dermis
- Well-developed lesions show layers of altered collagen (necrobiosis) alternating with layers of inflammation
- Inflammatory infiltrate
  - Giant cells, plasma cells, histiocytes, lymphocytes
- Perivascular inflammation
  - Mostly lymphocytes, sometimes plasma cells
- Fibrin may be present within vessels
- Epithelioid granulomas (may predominate in occasional cases) or cholesterol clefts may be present
- May extend into subcutaneous tissue
  - May see septal fibrosis or vascular changes (thickened walls, thrombosis, perivascular lymphocytes)

**DIFFERENTIAL DIAGNOSIS****Granuloma Annulare**

- Clinical
  - Pink papules
  - Tend to form annular arrangements
  - Tend to affect dorsal hands/feet/forearms/lower legs
- Histopathologic
  - Areas of altered collagen tend to be encircled by palisading histiocytes
  - Altered collagen interspersed with mucin
  - Giant cells and plasma cells often not prominent
  - Tends to be centered in dermis
    - Exception is deep granuloma annulare

**Necrobiotic Xanthogranuloma**

- Clinical
  - Yellow-orange plaques
  - Tend to be periorbital, but various sites can be affected
  - Associated with paraproteinemia
- Histopathologic
  - Irregular areas of altered collagen
  - Interspersed inflammation
    - Often includes unusual giant cells
  - Cholesterol clefts

**Rheumatoid Nodule**

- Clinical
  - Subcutaneous/dermal nodules, often adjacent to joints
- Histopathologic
  - Often centered in subcutaneous or deep dermis
  - Palisades of histiocytes surrounding central fibrin

**Sarcoidosis**

- Clinical
  - Protean manifestations
- Histopathologic
  - Classically epithelioid granulomas without palisading

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# Foreign Body Granuloma

## KEY FACTS

### TERMINOLOGY

- Granulomatous inflammation as response to traumatically introduced substances

### CLINICAL ISSUES

- Firm, usually colorless nodule that may or may not be painful or tender
- Often freely movable and can migrate from original site of introduction
- Removal of foreign body is curative

### MICROSCOPIC

- Giant cells, histiocytes, and lymphocytes forming granulomas surrounding foreign material
- Foreign body material is in most cases easily recognizable on H&E sections
  - Polarized light microscopy may help identify polarizable material in cases without obvious foreign material

- However, sarcoidosis can also have polarizable material, so identification of polarizable foreign material is not pathognomonic of foreign body granuloma (FBG)

### TOP DIFFERENTIAL DIAGNOSES

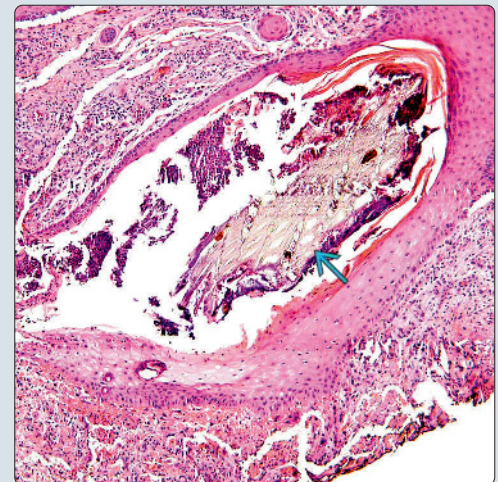
- Sarcoidosis
  - Birefringent foreign material can be seen in both sarcoidosis (up to 77% of cases) and FBG
  - Careful clinicopathologic correlation required to make correct diagnosis
- Infectious granulomatous diseases
  - Careful search on high power for organisms always warranted
  - Special stains (differ depending on organism of interest) on tissue may be confirmatory
- Ruptured cyst of follicle
  - Keratinized squamous cells rather than foreign material should be seen

### Erythema and Swelling

(Left) Foreign body granuloma of several months' duration is shown between the toes of a tennis player. A sliver of wood is the site of entry with surrounding erythema and swelling where granulation tissue is building up. (Right) High-power view shows foreign body granuloma due to a wood splinter. Note how the skin is walling off the foreign body so that it can eventually be extruded. (Courtesy L. Coleman, MD.)

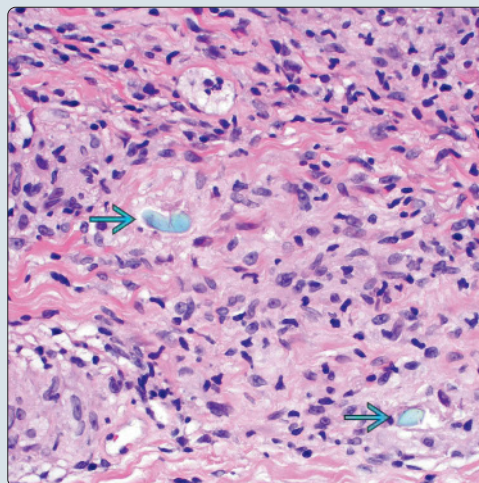


### Walling Off of Wood Splinter

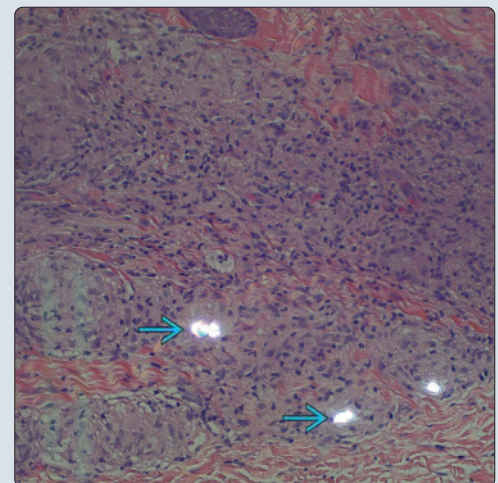


### Sarcoidal Granulomatous Dermatitis

(Left) A sarcoidal granulomatous dermatitis surrounds several small fragments of blue-green foreign material. (Right) Polarizing microscopy confirms the presence of foreign material when refractile, acellular fragments are seen.



### Polarizing Microscopy of Foreign Material





## TERMINOLOGY

### Abbreviations

- Foreign body granuloma (FBG)

### Definitions

- Granulomatous inflammation as response to traumatically introduced substances
  - Occurs in dermis, subcutaneous tissue, or soft tissue

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- Most common substances that elicit FBG response are lipids, wood, petrolatum, paraffin, lead, ink (tattoos), silica, silicone, talc, zirconium (deodorants), insect fragments (e.g., from tick bites)
- Suture (unremoved, undissolvable, or dissolvable but fails to dissolve)
- Shrapnel, bullets, and other war-related debris
- Can be caused by virtually any nondissolvable material too large for macrophages to carry away

### Other

- Endogenous material such as ingrown hair or keratin (degenerated cyst)

## CLINICAL ISSUES

### Presentation

- Firm, usually colorless nodule that may or may not be painful or tender
- Often freely movable and may have migrated from original site of introduction
- If acute for days to weeks, then more apt to be red, tender, and painful
- If longstanding, may mimic cutaneous malignancy
  - Can be especially problematic in patients with history of previous malignancy

### Treatment

- Removal of foreign body is curative
- May scar depending on size and site

### Prognosis

- Very rarely, malignancy may arise in FBGs (especially tattoo ink)

## MICROSCOPIC

### Histologic Features

- Giant cells, histiocytes, and lymphocytes forming caseating or noncaseating granulomas surrounding foreign material
  - Foreign body material may be easily recognizable on H&E sections (most cases)
  - Polarized light microscopy may help identify polarizable material in cases without obvious foreign material
    - However, sarcoidosis can also have polarizable material, so identification of polarizable foreign material is not pathognomonic of FBG
- Older lesions can show fibrosis or sclerosis
- Foreign body material commonly identified
  - Suture material, wood, silica, tattoo ink, talc, starch

## ANCILLARY TESTS

### Special Stains

- GMS and AFB stains should be performed on all cases of granulomas in skin to rule out infectious cause

## DIFFERENTIAL DIAGNOSIS

### Histological

- Sarcoidosis
  - Birefringent foreign material can be seen in both sarcoidosis (up to 77% of cases) and FBG
    - Careful clinicopathologic correlation required to make correct diagnosis
  - Similar histology of noncaseating granulomas composed of epithelioid histiocytes with multinucleated giant cells
- Infectious granulomatous diseases
  - Mycobacterial diseases such as TB, leprosy, and atypical mycobacterial diseases should always be considered
  - Deep fungal infections such as histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, blastomycosis, chromomycosis, others
    - Often pseudoepitheliomatous hyperplasia (PEH), but PEH can also be seen in FBG due to tattoo ink
    - Careful search on high power for organisms always warranted
  - Leishmaniasis, tularemia, and others can also form granulomas in skin
  - Histology often shows caseating granulomas with central necrosis (especially TB), but may only show noncaseating granulomas mimicking FBG or sarcoid
    - Culture may be necessary to identify organism
    - Special stains (differ depending on organism of interest) on tissue may be confirmatory
- Ruptured cyst or follicle (keratin granuloma)
  - Foreign body giant cell reaction can be seen in degenerated cysts (most commonly epidermal)
    - Keratinized squamous cells rather than foreign material should be seen
    - Masson stain will stain keratin red if diagnosis is in question (rarely needed)
  - Obvious foreign body material often seen in most cases of FBG; usually not difficult differential
- Clinical
  - Deep fungal infection
    - Careful search for fungal organisms always warranted for granulomatous inflammatory infiltrates
      - Special stains may be necessary to help identify organisms
  - Squamous cell carcinoma
    - Irregular indurated edge with central hyperkeratosis, ulceration, or crust
    - Loss of maturation, cytologic atypia, mitoses

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## Rheumatoid Nodule

## KEY FACTS

## CLINICAL ISSUES

- Occurs in 20-30% of RA patients
  - Most common cutaneous manifestation of RA
- Flesh-colored, asymptomatic 1- to 2-cm nodules over extensor joints, especially hands

## MICROSCOPIC



- Hallmark is nodules of palisading granulomas with central homogeneous, eosinophilic, fibrinoid necrobiotic collagen
- Granuloma composed of histiocytes and lymphocytes, usually located in deep dermis and subcutaneous tissue
- Larger nodules are multilocular with connections between necrotic centers
- Often perivascular lymphocytic infiltrates
- Significant stromal fibrosis is usually present

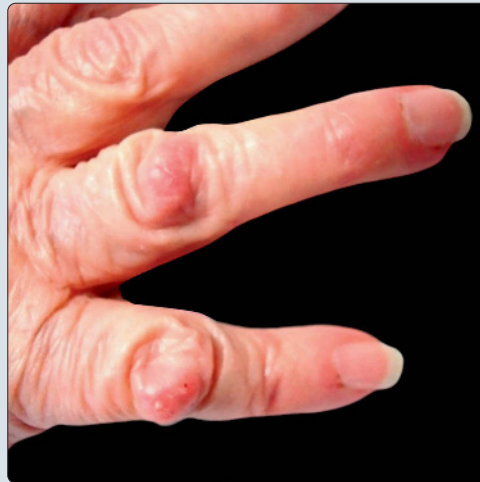
## TOP DIFFERENTIAL DIAGNOSES

- Deep or subcutaneous granuloma annulare
  - Often has less complete palisade (vs. RNs)

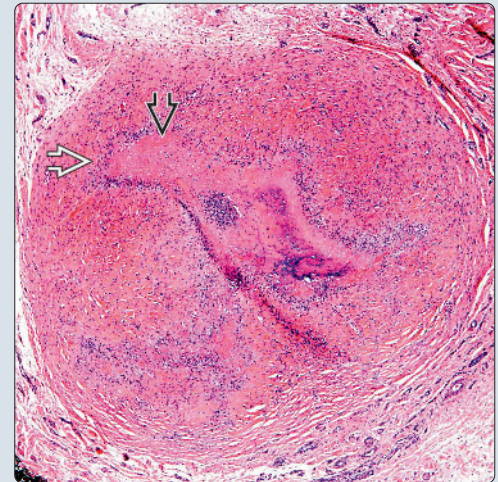
- Paler, blue edematous necrobiosis with mucin deposition and less stromal fibrosis
- Necrobiosis lipoidica
  - Characteristic layers of necrobiosis alternating with inflammation horizontally oriented to epidermis
- Rheumatic fever nodules
  - Clinically small, pea-sized nodules associated with rheumatic fever
  - Histology shows central necrosis with little histiocytic or lymphocytic infiltration
- Palisading neutrophilic granulomatous dermatitis
  - Early lesions show leukocytoclastic vasculitis
  - Older lesions show palisaded and granulomatous dermatitis with central basophilic necrotic areas similar to GA
- Epithelioid sarcoma "distal type"
  - Poorly circumscribed (vs. RN) granulomatous nodules often with central necrosis

Firm Pink Nodules Over Proximal Interphalangeal Joints



(Left) Firm pink nodules are shown over the proximal interphalangeal (PIP) joints of the 4th and 5th digits in this woman with rheumatoid arthritis. (Right) Classic appearance of RN shows a discrete nodule of fibrous tissue in the subcutis composed of a central area of red necrobiosis  and palisading histiocytes . (Courtesy L. Coleman, MD.)

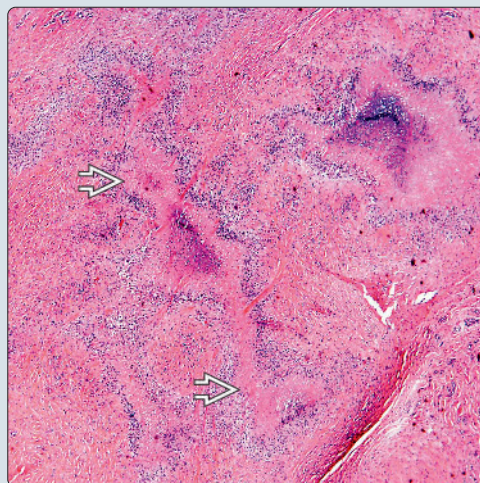


Discrete Nodule in Subcutis With Necrobiosis and Palisading Histiocytes

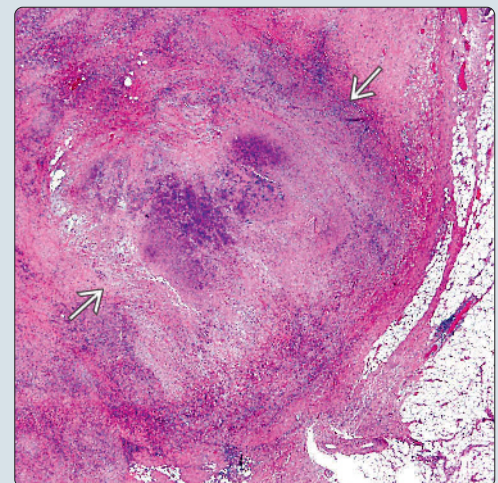


Multilocular Nodule With Connections Between Palisading Histiocytes

(Left) Low-power view of a very large, multilocular RN demonstrates connections between the palisading histiocytes and red necrotic centers . (Courtesy L. Coleman, MD.) (Right) Histologically, low-power epithelioid sarcoma can mimic RN, but the granulomatous nodules  are typically more poorly circumscribed and stain positive for CK-PAN. (Courtesy L. Layfield, MD.)



Poorly Circumscribed Granulomatous Nodule of Epithelioid Sarcoma



## TERMINOLOGY

### Abbreviations

- Rheumatoid nodule (RN)

### Definitions

- Firm nodules in skin seen in association with rheumatoid arthritis (RA)

## ETIOLOGY/PATHOGENESIS

### Unknown

- Endothelial damage at sites of trauma with resultant immune-complex disease is most common theory
- Commonest extraarticular manifestation of RA
- Complement activation is thought to play role in necrobiosis

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Occurs in 20-30% of RA patients
  - Most common cutaneous manifestation of RA

### Presentation

- Flesh-colored, asymptomatic 1- to 2-cm nodules over extensor joints, especially hands
- Rare occurrence at other sites such as tendons, vocal cords, lungs, heart, sclera, dura, bones, and peritoneum
- Rare cutaneous sites include nose and ears

### Treatment

- Not necessary, and RN not necessarily associated with response of rheumatoid arthritis to treatment

### Prognosis

- Associated with increased rheumatoid vasculitis and possibly worse RA
- May shrink, persist, or worsen
- May worsen rapidly (accelerated nodulosis) in response to methotrexate or TNF- $\alpha$  therapy

## MICROSCOPIC

### Histologic Features

- Hallmark is nodules of palisading granulomas with central homogeneous, eosinophilic, fibrinoid necrobiotic collagen
  - Granuloma composed of histiocytes and lymphocytes, usually located in deep dermis and subcutaneous tissue
- Significant stromal fibrosis is usually present
- Interstitial neutrophilia, vasculitis and pauci-inflammatory vascular thrombosis also commonly seen on biopsy
- Often perivascular lymphocytic infiltrates
- Larger nodules are multilocular with connections between necrotic centers

## ANCILLARY TESTS

### Serologic Testing

- Rheumatoid factor (RF) almost always found in high titers in patients with RNs

## DIFFERENTIAL DIAGNOSIS

### Histologic

- Deep or subcutaneous **granuloma annulare** (GA, pseudorheumatoid nodule)
  - Often has less complete palisade (vs. RNs)
  - Usually younger patients with no history of RA
  - Paler, blue edematous necrobiosis with mucin deposition and less stromal fibrosis
- **Necrobiosis lipidica**
  - Clinically typically affects shins of female diabetics
  - Characteristic layers of necrobiosis alternating with inflammation horizontally oriented to epidermis
- **Rheumatic fever nodules**
  - Clinically small, pea-sized nodules associated with rheumatic fever
  - Limited disease in children; RF factor negative and bone erosions are typically absent
  - Histology shows central necrosis with little histiocytic or lymphocytic infiltration
- **Palisading neutrophilic granulomatous dermatitis**
  - Papules, plaques, or linear cords symmetrically on trunk or extremities
  - Older lesions show palisaded and granulomatous dermatitis with central basophilic necrotic areas similar to GA
  - Central necrotic areas contain mucin (absent in RA) similar to GA
- **Epithelioid sarcoma "distal type"**
  - Clinically may also present as firm nodule on distal extremities of young adults
    - Usually no clinical history of RA
  - Irregular nodules of uniform epithelioid or polygonal cells with surrounding desmoplastic stroma
    - Occasional mitoses should be appreciable
  - Poorly circumscribed (vs. RN) granulomatous nodules often with central necrosis
  - Pancytokeratin (AE1/AE3, CAM5.2) and EMA positive, frequent loss of INI1
  - **Poor prognosis**; important not to miss

### Clinical

- **Granuloma annulare**
  - Tends to be annular vs. nodules of RN
  - RNs are over joints and on ears
    - GA usually not localized or restricted to those areas only (usually multiple lesions)
- **Rheumatoid nodulosis**
  - Only difference from RNs is clinical
    - No concomitant joint disease and may precede polyarthritis
- **Benign rheumatoid nodules**
  - Found in healthy, RF negative children (usually < 18 years of age) with no associated joint disease
  - Histologically indistinguishable from RNs in RA

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## KEY FACTS

### TERMINOLOGY

- Synonyms include actinic granuloma of O'Brien and annular elastolytic giant cell granuloma

### CLINICAL ISSUES

- Photodistributed, annular plaques with elevated borders and atrophic centers
- Chronic persistent condition that is often refractory to treatment
- Most common sites of involvement are dorsal hands, forearms, neck, and shins
- Most patients middle-aged or elderly adults

### MICROSCOPIC

- Classically, fibrotic areas with total loss of normal elastic tissue surrounded by giant cell granulomas with elastophagocytosis (engulfment of fragmented elastotic material)

### ANCILLARY TESTS

- Elastic stains such as Verhoeff-van Gieson and acid orcein highlight elastic tissue

### TOP DIFFERENTIAL DIAGNOSES

- Granuloma annulare
  - Mucin, necrobiosis, and preserved elastic material favor palisading granuloma annulare
- Sarcoidosis
  - Ultimately requires clinical evaluation for distinction
- Granulomatous slack skin
  - Shows dense diffuse dermal infiltrate of numerous histiocytes and multinucleated giant cells and atypical, convoluted lymphocytes

### DIAGNOSTIC CHECKLIST

- Significant histologic overlap with granuloma annulare may occur
- Elastophagocytosis is nonspecific histologic feature

Annular Plaques With Atrophic Centers



Actinic granuloma presents as annular plaques with atrophic centers and elevated borders on sun-exposed skin. (Courtesy S. Hsu, MD.)

**TERMINOLOGY****Abbreviations**

- Actinic granuloma (AG)

**Synonyms**

- Annular elastolytic giant cell granuloma (AEGCG), annular elastolytic granuloma (AEG), granuloma multiforme, actinic granuloma of O'Brien, Miescher granuloma of face

**Definitions**

- Asymptomatic eruption of annular plaques on sun-damaged skin with histology most often demonstrating interstitial granulomas

**ETIOLOGY/PATHOGENESIS****Theories**

- Different theories regarding pathophysiology have been set forth by authors
  - O'Brien proposed "actinic hypothesis" that actinic radiation results in damaged elastotic fibers, which then become target of specific autoimmune elastolytic or resorptive response by giant cell granulomas in AG
  - Given that some references have described actinically degenerate elastic internal elastic laminae as basis of temporal arteritis (giant cell arteritis), this idea is supported by clinical association between temporal arteritis, polymyalgia rheumatica, and AG
- However, other authors including Ackerman argued that elastolytic granuloma is not specific autoimmune finding but rather consequence of primary pathologic granulomatous processes, such as granuloma annulare (GA)
  - Demonstration of elastolytic granulomas in GA and other diseases supports concept of AG as GA on sun-damaged skin
- Terms AEG and AEGCG were put forth to describe histopathologic and clinical appearance described in AG, but without implying causal relationship with sun exposure
  - Terms such as Miescher granuloma of face and granuloma multiforme represent same condition

**CLINICAL ISSUES****Epidemiology**

- Age
  - Most patients middle-aged or elderly adults

**Site**

- Most common sites of involvement are dorsal hands, forearms, neck, and shins

**Presentation**

- Presents with annular or ring-shaped erythematous patches or plaques on photoexposed areas
- Borders of lesions are elevated and extend peripherally, while center becomes slightly atrophic
- Lesions are asymptomatic, but cosmetic disfigurement may result from lesions on head and neck
- Diabetes has been commonly associated condition in reports and retrospective studies

**Treatment**

- Drugs

- Rare condition without high-quality evidence to support effective treatments
- Anecdotally, successful treatment with pentoxifylline, acitretin and isotretinoin, hydroxychloroquine, and topical and oral corticosteroids has been reported

**Prognosis**

- Chronic persistent condition that is often refractory to treatment

**MICROSCOPIC****Histologic Features**

- When considered distinct from GA, tissue changes of AG consistently demonstrate granulomatous infiltrate, elastolysis, and elastophagocytosis in mid dermis
  - Central zone of lesion has fibrosis and lacks elastic tissue
  - Peripheral zone contains granulomas consisting of multinucleated giant cells with engulfed fragmented elastotic fibers (elastophagocytosis)
  - 3rd outer zone of uninvolved skin surrounds lesion
  - In contrast to GA, palisading histiocytes, necrosis, and interstitial mucin are absent
- Histologic subtypes of AG include classic giant cell annular form, vascular or necrobiotic form, histiocytic, and sarcoidal
  - Vascular or necrobiotic form, which has also been referred to as granuloma multiforme, demonstrates foci of necrobiosis without mucin and loss of elastic tissue surrounded by nonpalisading granulomas with elastophagocytosis
  - In sarcoidal variant, epithelioid histiocytes form tight granulomas with sparse inflammation in upper dermis with loss of elastic tissue throughout dermis
- Unique histologic features reported in association with AG include squamous syringometaplasia (squamous metaplasia of eccrine glands), pseudoepitheliomatous hyperplasia, and dilated follicular infundibula corresponding to open comedones
- Hybrid lesions, featuring elastolytic granulomas as well as palisading granulomas with necrobiosis, like those of GA, have been reported and suggest that AG and GA exist on histologic spectrum
- Elastophagocytosis is not specific feature and may also be found in dermal elastolysis and anetoderma, infections including leprosy and blastomycosis, neoplasms such as atypical fibroxanthoma and keratoacanthoma, and morphea and lichen sclerosus

**ANCILLARY TESTS****Histochemistry**

- Elastic stains such as Verhoeff-van Gieson (VVG) and acid orcein highlight elastic tissue, although they are not specific for damaged elastic fibers, which may underlie pathogenesis

**Immunohistochemistry**

- Giant cells of AG are intensely positive for lysozyme, while mononuclear histiocytes of AG and GA are nonreactive

**DIFFERENTIAL DIAGNOSIS****Granuloma Annulare**

- Histiocytes arranged interstitially between collagen fibers are common to both GA and AG
- AG has marked absence of normal elastin, solar elastotic material, and phagocytosis of fragmented elastotic material in giant cells
- Mucin, necrobiosis, and preserved elastic material favor palisading GA
- Often clinically indistinguishable from AG (other than distribution of lesions)
- Multinucleated giant cells can be seen in both but more common in AG
- Cases with significant overlap are well described

**Sarcoidosis**

- Sarcoidal variant may be histologically indistinguishable from sarcoidosis
- Ultimately requires clinical evaluation for distinction
- Elastophagocytosis may be present in both disorders, although loss of elastotic and normal elastic fibers is supportive of AG

**Granulomatous Slack Skin and Granulomatous Mycosis Fungoides**

- Granulomatous slack skin (GSS) is distinct rare clinical variant of mycosis fungoides, unlike granulomatous mycosis fungoides (GMF), which is simply histologic variant
- GSS shows dense diffuse dermal infiltrate of numerous histiocytes and multinucleated giant cells and atypical, convoluted lymphocytes
  - Giant cells engulf fragmented elastic fibers (elastophagocytosis) and lymphocytes, and there is marked loss of elastin
  - Epidermotropism and Pautrier microabscesses may be present as well
  - Clinical appearance is unique, with bulky pendulous plaques developing in skin folds
- GMF shows similar though less dramatic histologic features, and clinical features are those of other forms of mycosis fungoides, such as
  - Patches, plaques, and nodules

**DIAGNOSTIC CHECKLIST****Clinically Relevant Pathologic Features**

- Central zone with scar-like fibrosis and loss of normal elastic fibers
- Peripheral zone of multinucleated giant cells and elastophagocytosis (engulfment of fragmented elastotic material)
- Palisaded, necrobiotic, or sarcoidal granulomas are variably present

**Pathologic Interpretation Pearls**

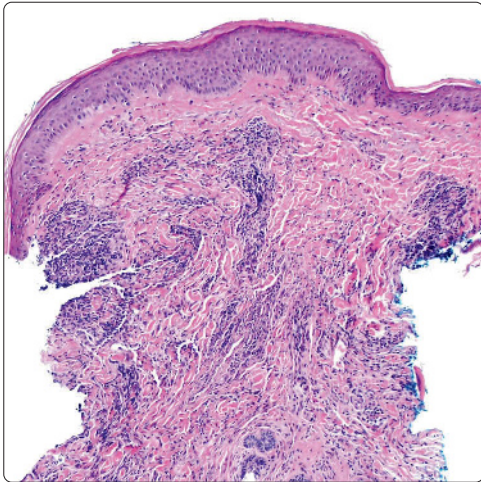
- Significant histologic overlap with GA may occur, and AG is best regarded as GA on sun-damaged skin
- Elastophagocytosis is nonspecific feature present in multiple granulomatous and nongranulomatous disorders

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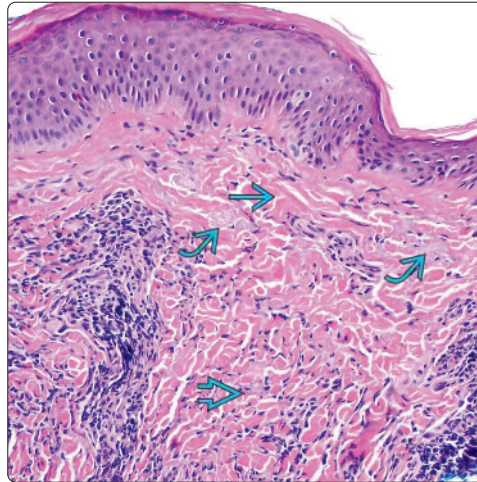
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**Interstitial Granulomatous Dermatitis**

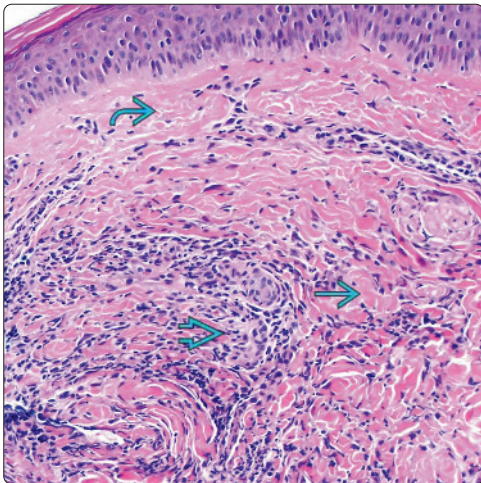


**Interstitial Granulomatous Dermatitis With Solar Elastosis**

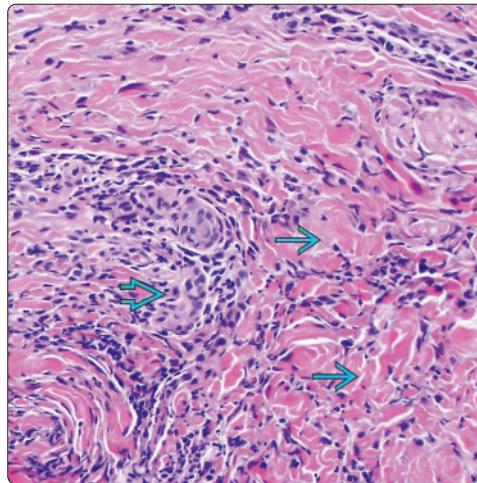


(Left) Low-power view of actinic granuloma demonstrates an interstitial granulomatous dermatitis on sun-damaged skin. (Right) Biopsy of actinic granuloma demonstrates an interstitial granulomatous dermatitis surrounded by a zone of uninvolved skin. Note the background solar elastosis.

**Interstitial Granulomas Surrounding Fibrosis**

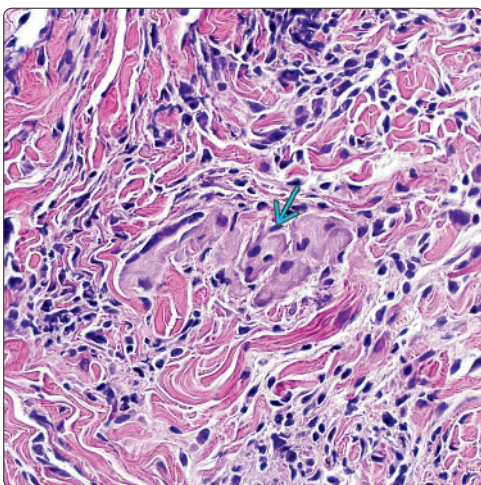


**Central Fibrosis and Peripheral Granulomas**

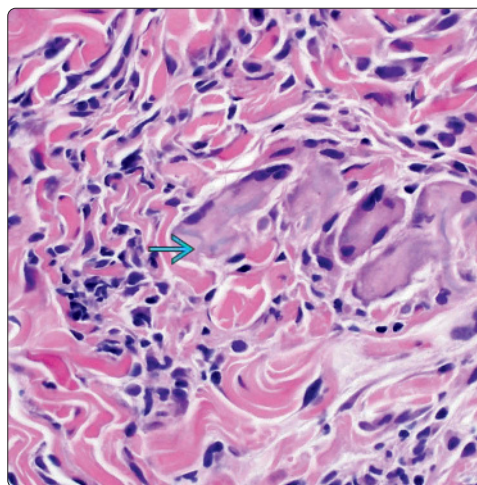


(Left) Actinic granuloma shows interstitial granulomas surrounding central fibrosis. A zone of uninvolved skin surrounds the granuloma. (Right) H&E shows central zone with fibrosis and loss of elastic fibers (elastolysis) surrounded by peripheral zone of interstitial granulomas with multinucleated giant cells.

**Multinucleated Giant Cells**



**Elastophagocytosis**



(Left) Actinic granuloma shows a peripheral zone with interstitial granulomas and multinucleated giant cells. (Right) Elastophagocytosis is often present but is a nonspecific finding.



# Annular Elastolytic Giant Cell Granuloma

## KEY FACTS

### TERMINOLOGY

- Granulomatous infiltrate with phagocytosis and destruction of elastic fibers
- Some authors contend that annular elastolytic giant cell granuloma is not unique diagnosis

### CLINICAL ISSUES

- Erythematous papules and plaques, which are often annular anywhere on body
- Most patients > 40 years of age
- Distributed anywhere on body
- No gender predilection

### MICROSCOPIC

- 3 zones
  - Central: Solar elastosis present without inflammation
  - Middle: Histiocytes and multinucleated giant cells (MNGCs) present with elastic fiber phagocytosis and elastolysis

- Outer zone: Elastic fibers are absent
- Necrobiosis and mucin deposition are absent
- Surrounding actinic damage is typically minimal

### ANCILLARY TESTS

- Elastic van Gieson
  - Central zone: Normal quantity and quality of elastic fibers
  - Middle zone: Elastic fibers within MNGCs and elastic fiber fragmentation
  - Outer zone: Absent staining

### TOP DIFFERENTIAL DIAGNOSES

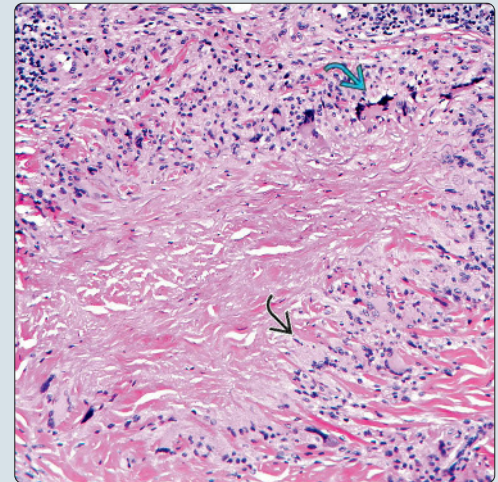
- Actinic granuloma of O'Brien
- Atypical necrobiosis lipoidica (Miescher granuloma)
- Granuloma annulare
- Sarcoidosis
- Squamous cell carcinoma
- Mid-dermal elastolysis

**Yellow-Orange Plaques**

(Left) Multiple yellow-orange annular plaques on the upper trunk of this patient clinically mimic necrobiosis lipoidica. The patient did not have diabetes, and the biopsy was compatible with annular elastolytic giant cell granuloma (AEGCG). (Right) AEGCG is characterized by a histiocytic infiltrate with multinucleated giant cells. Palisading may be present.

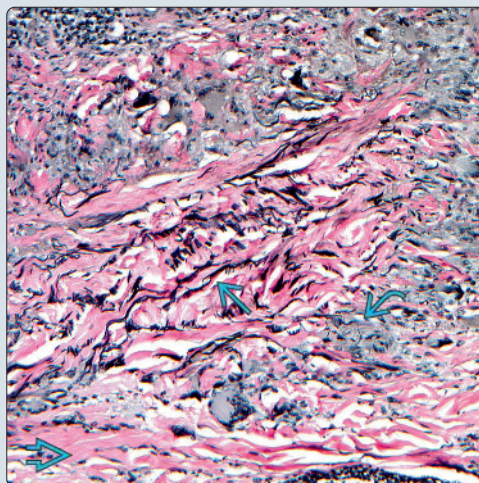


**Palisaded Granuloma**

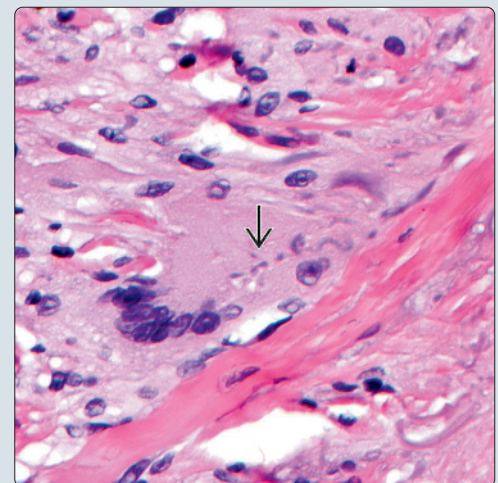


**Three Zones of Elastic Fiber Deposition**

(Left) Three zones are highlighted with an elastin stain. The central portion has elastic fibers with surrounding histiocytes and elastophagocytosis (middle zone). The outer zone has absent elastic fibers. (Right) Phagocytosis of elastic fibers can be seen within the multinucleated giant cells.



**Phagocytosis**



**TERMINOLOGY****Abbreviations**

- Annular elastolytic giant cell granuloma (AEGCG)

**Synonyms**

- Giant cell elastophagocytosis

**Definitions**

- Granulomatous infiltrate with phagocytosis and destruction of elastic fibers
  - Typically arising in areas with minimal actinic damage
- Some authors contend that AEGCG is not unique diagnosis
  - AEGCG is term for spectrum that includes other individual diagnoses
    - Granuloma annulare
    - Actinic granuloma of O'Brien
    - Atypical necrobiosis lipoidica
    - Granuloma multifforme

**CLINICAL ISSUES****Epidemiology**

- Age
  - Most > 40 years of age
- Sex
  - No gender predilection

**Site**

- Distributed anywhere on body

**Presentation**

- Erythematous papules and plaques, which are often annular

**Treatment**

- Surgical approaches
  - Excision has been curative in some cases
- Drugs
  - Treatment is often empirical
  - Multiple drugs including hydroxychloroquine, corticosteroids, PUVA, cyclosporine, topical tacrolimus/pimecrolimus, doxycycline/minocycline, and others have been used with varying success

**Prognosis**

- Spontaneous cure has been reported

**MICROSCOPIC****Histologic Features**

- 3 zones
  - Central: Solar elastosis present without inflammation
  - Middle: Histiocytes and multinucleated giant cells (MNGCs) present with elastic fiber phagocytosis and elastolysis
    - Diffuse infiltrate ± palisading
    - Lymphocytes present, but may also see eosinophils and plasma cells
  - Outer: Elastic fibers are absent
- Necrobiosis and mucin deposition are absent
- Surrounding actinic damage is typically minimal

**ANCILLARY TESTS****Histochemistry**

- Elastic van Gieson
  - Elastic fibers will stain darkly
    - Central zone: Normal quantity and quality of elastic fibers
    - Middle zone: Elastic fibers within MNGCs and elastic fiber fragmentation
    - Outer zone: Absent staining

**DIFFERENTIAL DIAGNOSIS****Histological**

- **Granuloma annulare**
  - Palisading histiocytes and MNGCs around central mucin accumulation
  - Necrobiosis is present
  - Fewer nuclei in MNGCs
- **Atypical necrobiosis lipoidica (Miescher granuloma)**
  - No scarring, necrobiosis, or dermal mucin deposition
- **Mid-dermal elastolysis**
  - Histiocytes and MNGCs in mid dermis
  - Absence of elastic fibers, but elastophagocytosis has been reported

**Clinical**

- **Actinic granuloma of O'Brien**
  - Reserved for lesions arising in areas of heavy solar elastosis
  - Single or grouped pink papules or annular plaques on sun-exposed skin
    - Face, neck, chest, arms, etc.
  - Associated with temporal arteritis
  - Controversial entity: Some consider it granuloma annulare on sun-exposed skin
- **Atypical necrobiosis lipoidica (Miescher granuloma)**
  - Annular lesions of face and scalp
  - Predominantly in females
- **Granuloma annulare**
  - Most often over bony prominences
  - Biopsy necessary to differentiate
- **Sarcoidosis**
  - Apple jelly color
  - Biopsy necessary to differentiate
- **Squamous cell carcinoma**
  - Scale, crust, or ulcer present
  - Biopsy easily differentiates

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# Melkersson-Rosenthal Syndrome

## KEY FACTS

### TERMINOLOGY

- Melkersson-Rosenthal syndrome (MRS): Idiopathic triad of orofacial swelling (especially lips), facial nerve palsy (recurrent), and lingua plicata (fissured tongue, scrotal tongue)

### CLINICAL ISSUES

- 3 major clinical forms: Monosymptomatic (Miescher cheilitis), oligosymptomatic, and complete


### MICROSCOPIC

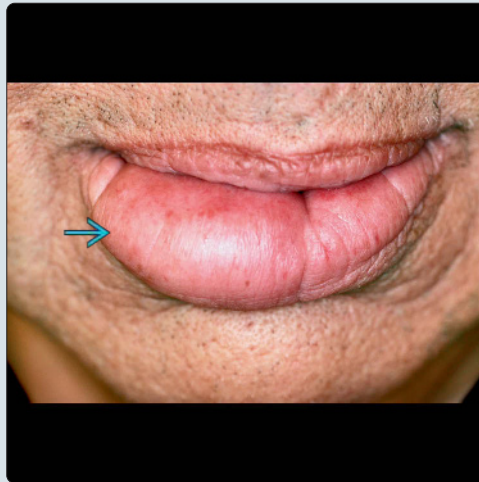
- Early lesions: Subepidermal edema, lymphocyte-predominant perivascular infiltrates
- Late lesions
  - Perivascular mononuclear cell infiltrate with noncaseating epithelioid granulomas, multinucleate giant cells, and surrounding lymphocytes, plasma cells, and macrophages
  - Diffuse stromal edema

### TOP DIFFERENTIAL DIAGNOSES

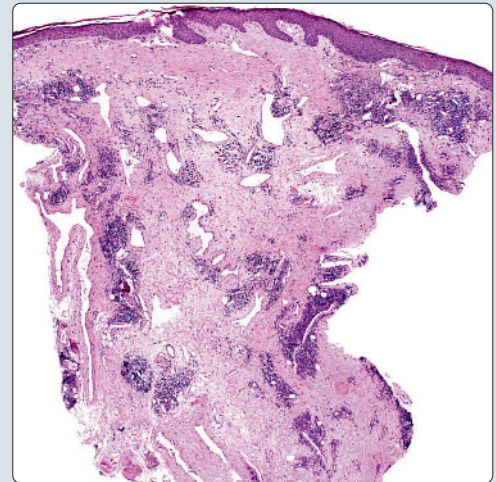
- Crohn disease (CD)
  - Lesions often ulcerated, often elevated C-reactive protein, and abnormal blood count
  - Patients may have associated gastrointestinal symptoms but oral involvement may be presenting sign
- Sarcoidosis
  - Often systemic or multifocal cutaneous involvement
    - Sarcoid limited to lip would be rare
- Foreign body reaction
  - Foreign material identified by light polarization
- Orofacial tuberculosis
  - Granulomas are typically caseating (central necrosis)
- Granulomatous rosacea
  - Dilated superficial capillaries, lymphohistiocytic or histiocytic infiltrate surrounding intact or ruptured follicles on histology

Lower Lip Swelling


(Left) Chronic swelling of the lip  is shown in a patient with cheilitis granulomatosa, which is part of the Melkersson-Rosenthal triad. (Right) Low-power view of Melkersson-Rosenthal syndrome demonstrates a superficial and deep perivascular granulomatous chronic inflammatory infiltrate and diffuse stromal edema.



Superficial and Deep Perivascular Granulomatous Dermatitis

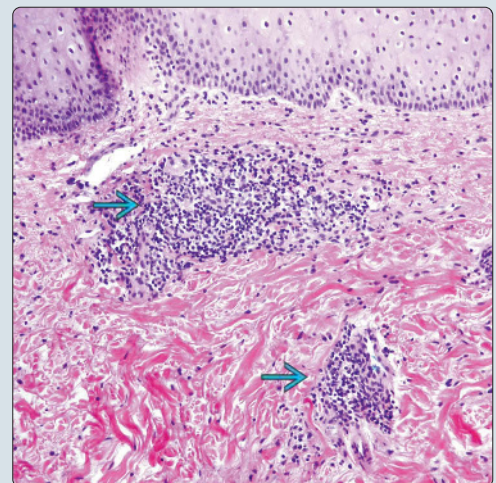


Swelling of Both Upper and Lower Lips in MRS

(Left) Chronic swelling of lips in a patient illustrates cheilitis granulomatosa, which is part of the Melkersson-Rosenthal triad. (Right) This is a case of cheilitis granulomatosa, which, along with Melkersson-Rosenthal syndrome, has been subsumed by the term orofacial granulomatosis. Note the nodular infiltrates of lymphocytes .



Nodular Infiltrate of Lymphocytes



## TERMINOLOGY

### Abbreviations

- Melkersson-Rosenthal syndrome (MRS)

### Synonyms

- Granulomatous cheilitis, cheilitis granulomatosa, Miescher-MRS
- Orofacial granulomatosis also includes Miescher cheilitis (monosymptomatic form of MRS), sarcoidosis, Crohn disease (CD), tuberculosis, and foreign body reactions

### Definitions

- MRS: Idiopathic triad of orofacial swelling (especially lips), facial nerve palsy (recurrent), and lingua plicata (fissured tongue, scrotal tongue)
- Miescher cheilitis: Granulomatous inflammation confined to lip
- Some regard oral CD as oligosymptomatic form of MRS
- Orofacial granulomatosis is clinicopathologic entity describing patients with oral noncaseating granulomatous lesions in absence of diagnosable sarcoidosis or CD
- Granulomatous cheilitis (cheilitis granulomatosa) is simply histopathologic description for these granulomatous processes occurring on and around lips

## CLINICAL ISSUES

### Presentation

- 3 major clinical forms: Monosymptomatic (Miescher cheilitis), oligosymptomatic, and complete
- Orofacial edema, facial nerve palsy, and fissured tongue seen in classic, complete form
  - Upper lip swelling typically has rapid onset, then gradual onset of lower lip swelling over months
- Granulomatous cheilitis on biopsy and 1 (monosymptomatic form) or 2 (oligosymptomatic form) clinical manifestations listed above constitute other forms of disease

### Treatment

- Intralesional corticosteroids or surgical repair may be helpful

### Prognosis

- Swelling of tongue is permanent
  - CD or sarcoidosis may develop later

## MICROSCOPIC

### Histologic Features

- Early lesions
  - Subepidermal edema
  - Lymphocyte predominant perivascular infiltrates
- Late lesions
  - Mononuclear perivascular lymphocyte-predominant infiltrates with some plasma cells and macrophages
  - Diffuse stromal edema
  - Noncaseating epithelioid granulomas, multinucleate giant cells, and surrounding lymphocytes, plasma cells, and macrophages

- Occasionally granulomas are not seen; well-demarcated, central lymphocytic nodule marginated by plasma cells and macrophages in edematous stroma is seen instead

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- CD
  - In children, oral involvement more likely to occur before CD is diagnosed
  - Lesions often ulcerated, often elevated C-reactive protein, and abnormal blood count
  - Patients may have associated gastrointestinal symptoms but oral involvement may be presenting sign
- Sarcoidosis
  - Often systemic or multifocal cutaneous involvement
    - Sarcoid limited to lip would be rare
  - Typically no stromal or subepidermal edema (vs. MRS)
- Foreign body reaction
  - Foreign material identified by light polarization
  - Sarcoidosis must be ruled out clinically
- Orofacial tuberculosis
  - Granulomas are typically caseating (central necrosis)
  - Organisms may be identified with special stains
  - Clinical history of TB exposure or travel to endemic country
- Granulomatous rosacea
  - Discrete, yellowish-brown papules on cheeks, nose, and perioral areas
  - Dilated superficial capillaries, lymphohistiocytic or histiocytic infiltrate surrounding intact or ruptured follicles on histology
    - Noncaseating granulomas may also be seen

### Clinical

- Cheilitis glandularis
  - Mainly affects minor salivary glands of lower lip
  - Histology shows variably dilated and tortuous minor salivary gland ducts with interstitial acute and chronic inflammation

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- In children, orofacial granulomatosis may be initial presentation of CD
  - Careful surveillance should be recommended in this patient population

### Pathologic Interpretation Pearls

- Classic triad of MRS is rarely seen
  - Mono- or oligosymptomatic forms are much more commonly seen

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## Multicentric Reticulohistiocytosis

## KEY FACTS

## TERMINOLOGY

- Histiocytic disorder often associated with underlying malignancy or with arthritis that can be mutilating

## CLINICAL ISSUES

- Tends to present in middle-aged adults
- Tends to affect lateral digits, dorsal hands, and periungual skin; latter may manifest so-called coral bead sign when multiple along nail fold (seen in ~ 20% in one study)
- Presents on skin in only 30%
  - ~ 30% have both skin and joint involvement at presentation; 40% present with arthritis alone

## MICROSCOPIC

- Dermal infiltrate of histiocytes and giant cells with abundant ground-glass cytoplasm (oncocytic)
  - Cytoplasm often 2-toned (darker and lighter areas)
- Histiocytes: Solitary nucleus; giant cells: 2-10 nuclei randomly distributed in cytoplasm or clustered at one end

## TOP DIFFERENTIAL DIAGNOSES

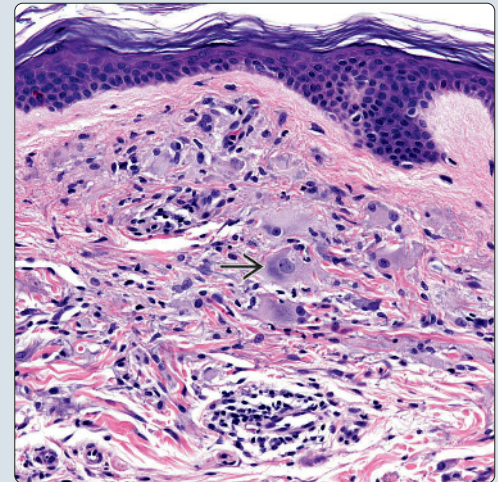
- Solitary reticulohistiocytoma
  - Histopathology similar to MRH
  - Solitary lesion clinically
  - Subtle differences from MRH that may be evident
    - Giant cells may have more nuclei
    - May be more cellular and sheet-like
- Juvenile xanthogranuloma
  - Clinically may be solitary or multiple
  - May have component of oncocytic histiocytes/giant cells
    - Has admixture of other cells
    - Histiocytic cells [vacuolated, xanthomatized (foamy), scalloped, spindle]

Pink-Red Firm Papules

**(Left)** This patient has multicentric reticulohistiocytosis (MRH). He has scattered pink-red, firm papules → mainly on the dorsal hands. He also had a recent onset of arthritis. (Courtesy K. Watsky, MD.) **(Right)** MRH typically shows oncocytic histiocytes and giant cells. Oncocytic cells → have abundant, 2-toned cytoplasm.

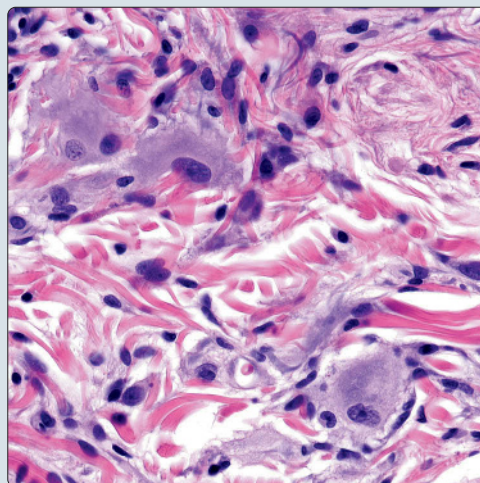


Oncocytic Histiocytes and Giant Cells

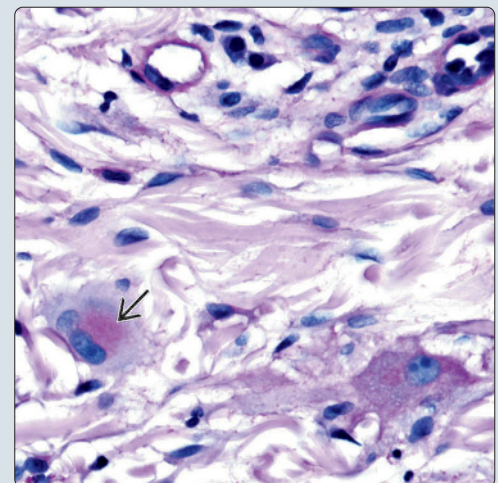


Abundant 2-Toned Cytoplasm

**(Left)** These oncocytic cells have abundant, 2-toned cytoplasm. **(Right)** The 2-toned cytoplasm of oncocytic histiocytes and giant cells shows 2 different colors with periodic acid-Schiff staining. There is a darker pink area → surrounded by paler, blue-pink cytoplasm.



2-Toned Cytoplasm





## TERMINOLOGY

### Abbreviations

- Multicentric reticulohistiocytosis (MRH)

### Definitions

- Histiocytic disorder often associated with underlying malignancy or with arthritis that can be mutilating

## CLINICAL ISSUES

### Epidemiology

- Age
  - Tends to present in middle-aged adults
- Sex
  - Female predominance

### Site

- Tends to affect lateral digits, dorsal hands, and periungual skin; latter may manifest so-called coral bead sign when multiple along nail fold (seen in ~ 20% in one study)
- May also affect ears and face (especially bordering nostrils)
- May be distributed widely over body
- May affect mucosa or, rarely, internal organs (e.g., lungs)
- Uncommonly, may have overlapping features with dermatomyositis

### Presentation

- Cutaneous: Presenting site in 30%
  - ~ 30% have both skin and joint involvement at presentation
  - Asymptomatic pink to red to yellow papules and nodules
  - Size: 0.3-2 cm
  - Xanthelasma-like lesions may be evident on eyelids in up to 25%
- Musculoskeletal: Presenting symptom is arthritis in 40%
  - Joints most commonly affected are interphalangeal joints; others commonly affected are knees, wrists, shoulders, and elbows

### Treatment

- Alkylating agents or other systemic agents in severe cases

### Prognosis

- Lesions may regress spontaneously over years (~ 7 years in one review)
- Joint destruction is permanent in advanced cases

### Associations

- Symmetric arthritis (may be mutilating = arthritis mutilans)
- Up to 25% of patients may have underlying malignancy
- Autoimmune thyroiditis
- Hyperlipidemia

## IMAGING

### Radiographic Findings

- Punched-out erosions are most typical

## MICROSCOPIC

### Histologic Features

- Dermal infiltrate of oncocyctic histiocytes and giant cells

### Cytologic Features

- Oncocyctic histiocytes and giant cells
  - Abundant ground-glass cytoplasm (oncocyctic)
  - Cytoplasm often 2-toned (darker and lighter areas)
  - Histiocytes: Solitary nucleus; giant cells: 2-10 nuclei randomly distributed in cytoplasm or clustered at one end

## ANCILLARY TESTS

### Histochemistry

- Periodic acid-Schiff
  - Staining pattern: Darker portion of cytoplasm of histiocytes and giant cells stains dark pink

### Immunohistochemistry

- CD68(+)
- CD1a(-)
- S100(-)
- Generally FXIIIA (-)

### Electron Microscopy

- Abundant mitochondria and lysosomes

## DIFFERENTIAL DIAGNOSIS

### Solitary Reticulohistiocytoma

- Clinical
  - Solitary lesion
  - Often on head or neck
  - No systemic associations
- Histopathologic
  - Similar to MRH
  - Subtle differences from MRH that may be evident
    - Giant cells may have more nuclei
    - May be more cellular and sheet-like
- Immunohistochemistry
  - CD68(+)
  - CD1a(-)
  - Rarely S100(+)

### Juvenile Xanthogranuloma

- Clinical
  - May be solitary or multiple
- Histopathologic
  - May have component of oncocyctic histiocytes/giant cells
  - Has admixture of other cells
    - Histiocytic cells [vacuolated, xanthomatized (foamy), scalloped, spindled]
    - Touton giant cells

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# Necrobiotic Xanthogranuloma

## KEY FACTS

### TERMINOLOGY

- Chronic, progressive, yellow to red to purple plaques and nodules, highly associated with paraproteinemia

### CLINICAL ISSUES

- Often periorbital
  - May affect other areas of face and body
- Red-purple to yellow-orange-brown plaques, papules, and nodules
- Size: 0.5-20 cm
- IgG-κ paraproteinemia most common
- 10-25% of patients progress to develop multiple myeloma
- Associated itching, burning, pain

### MICROSCOPIC

- Areas of altered dermal collagen (necrobiosis)
- Inflammatory infiltrate with histiocytes, Touton giant cells, and bizarre, atypical giant cells

- Cholesterol clefts, lymphoid nodules, involvement of panniculus not uncommon

### TOP DIFFERENTIAL DIAGNOSES

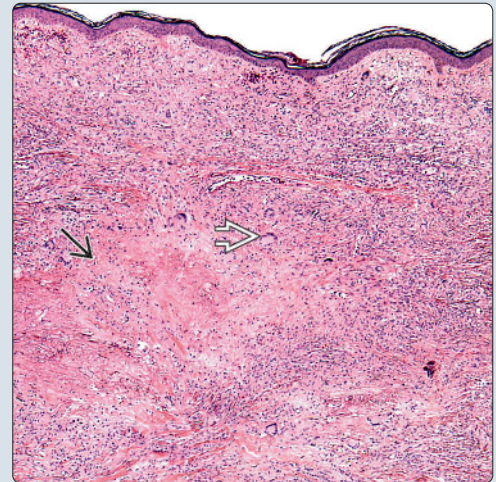
- Necrobiosis lipoidica
  - Tends to affect shins
  - Layers of altered collagen alternating with layers of inflammation
- Foreign body granuloma
  - Foreign material may be evident in giant cells
- Juvenile xanthogranuloma
  - Touton giant cells admixed with histiocytes, eosinophils
- Plane xanthoma
  - Foam cells in dermis
- Granuloma annulare
  - Palisades of histiocytes around altered collagen with mucin

**Yellow-Orange Papules and Plaques**

(Left) This patient's biopsy was compatible with necrobiotic xanthogranuloma. There are yellow-orange papules and plaques on the lower eyelid. (Right) In necrobiotic xanthogranuloma, there are broad zones of altered collagen (necrobiosis) surrounded by a cellular infiltrate. Giant cells are often prominent.

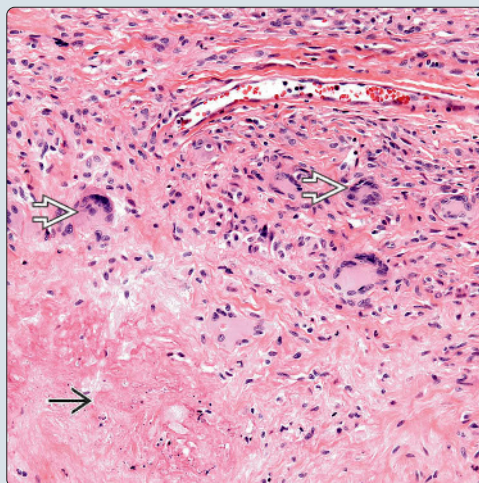


**Necrobiosis Surrounded by Inflammation**

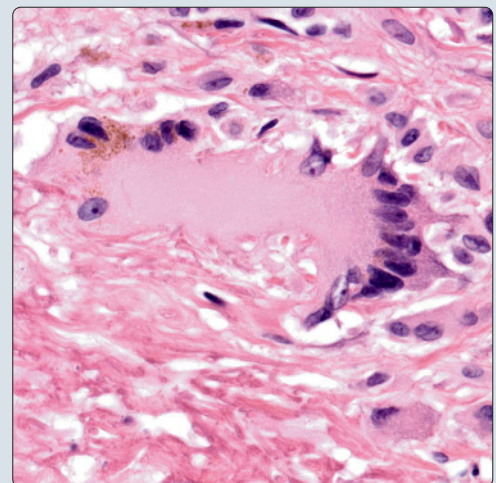


**Giant Cells at Periphery of Necrobiosis**

(Left) In this field of necrobiotic xanthogranuloma, there are numerous giant cells at the border of a zone of altered collagen. (Right) In necrobiotic xanthogranuloma, there may be bizarre or atypical giant cells, as shown here.



**Atypical Giant Cells**



## TERMINOLOGY

### Abbreviations

- Necrobiotic xanthogranuloma (NXG)

### Definitions

- Chronic, progressive, yellow to red to purple plaques and nodules, highly associated with paraproteinemia

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- Literature states that focus floating microscopy shows presence of *Borrelia* in some cases
- Unclear pathogenesis in most cases

## CLINICAL ISSUES

### Site

- Often periorbital
- May affect other areas of face and body

### Presentation

- Red-purple to yellow-orange-brown plaques, papules, and nodules
- Size: 0.5-20 cm
- Telangiectasias often present
- Lesions often ulcerate or scar
- Associated itching, burning, pain

### Laboratory Tests

- Immunofixation electrophoresis
  - IgG-κ paraproteinemia most common
  - IgG-λ or IgA paraproteinemia also described

### Treatment

- Difficult
- Systemic agents (e.g., melphalan)

### Prognosis

- Chronic and progressive
- 10-25% of patients progress to develop multiple myeloma

### Complications

- Ophthalmic
  - e.g., blepharoptosis, scleritis, keratitis
- Internal involvement
  - Heart
  - Lung
  - Kidney
  - Liver
  - Intestine
  - Spleen
  - Muscle
  - Ovary
  - Larynx
  - Pharynx
  - Skull

## MICROSCOPIC

### Histologic Features

- Areas of altered dermal collagen (necrobiosis)

- Inflammatory infiltrate with giant cells and histiocytes
  - Touton giant cells
  - Foreign body giant cells
    - May have bizarre appearance
- Cholesterol clefts
  - Histiocytes and giant cells may palisade around clefts
- Foamy cells
- Occasional lymphoid nodules, plasma cells, eosinophils
- May extend into panniculus (Touton cell panniculitis)

## ANCILLARY TESTS

### Immunohistochemistry

- Lymphocytes and plasma cells polytypic
- Histiocytes and giant cells are CD68(+), CD1a(-)

## DIFFERENTIAL DIAGNOSIS

### Necrobiosis Lipoidica

- Clinical
  - Tends to affect shins
- Histopathologic
  - Layers of altered collagen alternating with layers of inflammation
  - Less cellular than NXG with giant cells and plasma cells
    - Generally giant cells are not as bizarre or atypical as in NXG
    - Touton giant cells generally not prominent

### Foreign Body Granuloma

- Histopathologic
  - Foreign material may be evident in giant cells

### Juvenile Xanthogranuloma

- Clinical
  - Pink-yellow papule
- Histopathologic
  - Necrobiosis absent
  - Touton giant cells admixed with histiocytes, eosinophils

### Plane Xanthoma

- Clinical
  - May be associated with paraproteinemia
  - Flat yellow patch/plaque
- Histopathologic
  - Necrobiosis absent
  - Foam cells in dermis

### Granuloma Annulare

- Clinical
  - Pink papules that tend to form annular arrangements
- Histopathologic
  - Palisades of histiocytes around altered collagen with mucin

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## KEY FACTS

### TERMINOLOGY

- More appropriate term is periorificial dermatitis

### ETIOLOGY/PATHOGENESIS

- Skin barrier dysfunction, atopic diathesis, and corticosteroid use are associated but not definitively causative

### CLINICAL ISSUES

- Variant of rosacea that presents with papules around mouth, nose, and eyes

### MICROSCOPIC

- Spongiosis and perifollicular lymphohistiocytic infiltrates, ± granulomas

### ANCILLARY TESTS

- PAS and Fite or AFB stains may be useful in excluding infections

### TOP DIFFERENTIAL DIAGNOSES

- Sarcoidosis
  - Granulomas in sarcoidosis typically lack lymphocytic infiltrates seen in perioral dermatitis (POD) and granulomatous rosacea
- Granulomatous rosacea
  - Histologically, telangiectasia and marked solar elastosis are present in classic rosacea and granulomatous rosacea but absent in granulomatous periorificial dermatitis (GPD) and POD
- Lupus miliaris disseminatus faciei
  - Well-established lesions demonstrate caseating (tuberculoid) granulomas surrounded by giant cells with close relationship to damaged hair follicles
- Contact dermatitis
  - More significant spongiosis, usually with eosinophils and without perifollicular mixed infiltrates, distinguishes contact dermatitis from variants of rosacea including POD

Papules and Pustules Around Mouth



Perioral dermatitis is shown. Papules and pustules surround the mouth and nares in a child with a history of potent topical steroid usage.

## TERMINOLOGY

### Abbreviations

- Perioral dermatitis (POD)

### Synonyms

- Granulomatous periorificial dermatitis (GPD)
- Periorificial dermatitis

### Definitions

- Follicular acneiform process that presents with small inflammatory periorificial papules

## ETIOLOGY/PATHOGENESIS

### Unknown

- Skin barrier dysfunction and atopic diathesis are associated with POD but not definitively causative
- Corticosteroid use is linked to POD, and in study of children and adolescents, > 70% of patients had history of topical, inhaled, or systemic steroid use
- POD often improves with steroids and then rebounds or worsens upon discontinuation
- Fluorinated topical steroids are particularly associated with POD
- Oral contraceptive therapy as well as irritation due to cosmetics, toothpastes, and moisturizing creams have also been linked with POD

## CLINICAL ISSUES

### Epidemiology

- Age
  - Occurs in all age groups
  - Common in children and can even occur in infants
- Sex
  - Most common in adult women

### Site

- More appropriate term is periorificial dermatitis, since lesions are often distributed over perinasal and periocular areas
- Less common areas of involvement include cheeks, chin, forehead, and neck

### Presentation

- Pustules, papules, and vesicles are located around mouth, with sparing of narrow zone of uninvolved skin around vermilion border of lips
- Prominent eczematous component may also be present
- GPD is clinical variant of POD with predilection for young children of Afro-Caribbean descent
  - Lesions have red, brown, or yellow color

### Treatment

- Drugs
  - Following drugs have all been studied in treatment of POD
    - Topical pimecrolimus and tacrolimus
    - Topical and oral metronidazole
    - Topical and oral erythromycin
    - Oral tetracycline class antibiotics
    - Isotretinoin

- Based on evidence-based systematic review, most effective treatments are oral tetracycline class antibiotics, topical pimecrolimus, and topical erythromycin
- Of note, resolution without specific treatment often occurs when inciting irritant or topical steroid is avoided

### Prognosis

- POD is benign and often self-limited disease with good response to several widely available pharmacologic treatments

## MICROSCOPIC

### Histologic Features

- Histopathology of POD is often nonspecific and very similar to that of rosacea, with wide range of findings
- In contrast to classic examples of rosacea, eczematous features are often present
- All biopsies demonstrate mild spongiosis and parakeratosis with perivascular and periadnexal lymphohistiocytic infiltrate
- Additional variable features include neutrophils within follicular microabscesses or dermal infiltrates, giant cells, sarcoidal granulomas, and ruptured follicles with foreign body reaction

## ANCILLARY TESTS

### Histochemistry

- PAS and Fite or AFB stains may be useful in excluding infectious etiologies in specimens with granulomatous inflammation, particularly sarcoidal granulomas

## DIFFERENTIAL DIAGNOSIS

### Sarcoidosis

- Sarcoidosis may be difficult to discriminate from POD and granulomatous rosacea, but mixed infiltrates with plasma cells and neutrophils, perifollicular granulomas limited to superficial dermis, and epidermal changes are more commonly seen in POD and granulomatous rosacea
- Epithelioid granulomas are seen in all 3 diseases, but granulomas are often present in deep dermis in biopsies of sarcoidosis
- Additionally, granulomas in sarcoidosis typically lack lymphocytic infiltrates seen in POD and granulomatous rosacea

### Granulomatous Rosacea

- Histology of granulomatous rosacea is identical to that of GPD and may sometimes also be identical to that of POD
- Noncaseating granulomas with giant cells, lymphohistiocytic infiltrate, and prominent perifollicular accentuation are seen
- Pustules and ruptured follicles may also be present
- Therefore, GPD, granulomatous rosacea, and POD should be viewed as histologic variants that occur along spectrum but are associated with distinct clinical presentations
- Unlike GPD, granulomatous rosacea is rarely seen in childhood and is associated with persistent erythema and flushing of cheeks and central midface

- Histologically, telangiectasia and marked solar elastosis are present in classic rosacea and granulomatous rosacea but absent in GPD and POD

## Lupus Miliaris Disseminatus Faciei

- Lupus miliaris disseminatus faciei (LMDF) is also referred to as acne agminata and FIGURE (facial idiopathic granulomas with regressive involution)
  - It presents with yellow-brown papules of midface and periocular areas, is difficult to treat, and often heals spontaneously with mild scarring
- Well-established lesions demonstrate caseating (tubercloid) granulomas surrounded by giant cells with close relationship to damaged hair follicles
- Caseation has been historically described as unique finding in LMDF, but
  - Given that biopsies related to clinical presentations of LMDF may only show nonspecific perifollicular granulomas and that minority of cases of granulomatous rosacea feature caseation
    - LMDF may be considered to exist on histologic spectrum with other variants of rosacea

## Contact Dermatitis

- Clinical overlap may be significant but more significant spongiosis, usually with eosinophils and without perifollicular mixed infiltrates, distinguishes contact dermatitis from variants of rosacea including POD

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Perivascular and periadnexal lymphohistiocytic infiltrate
- Mild spongiosis and parakeratosis
- Sometimes pustules, perifollicular granulomas with giant cells, and ruptured follicles

### Pathologic Interpretation Pearls

- Often shows nonspecific features seen in other variants of rosacea
- Cases with granulomatous inflammation overlap with GPD, granulomatous rosacea, and LMDF

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**Periocular Papules and Pustules**

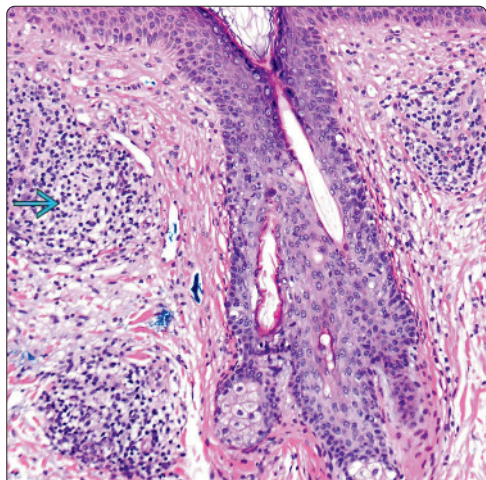


**Perioral Pink Papules Becoming Confluent**

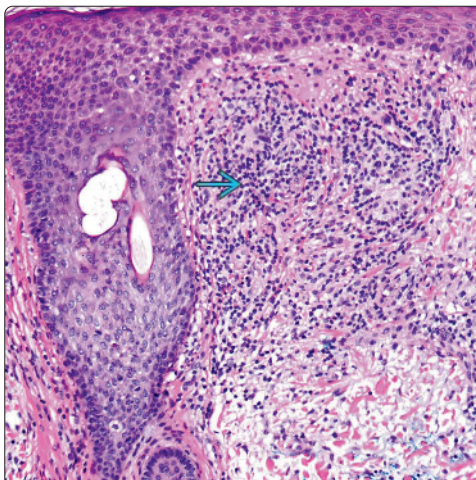


**(Left)** Periorificial dermatitis can also show periocular papules and pustules. **(Right)** Young girl with tiny pink papules becoming confluent in a case of perioral dermatitis is shown. A perioral halo of clear skin is present, and the papules only meet the lips at the angles of the mouth, which is quite typical of perioral dermatitis.

**Perifollicular Granulomas**

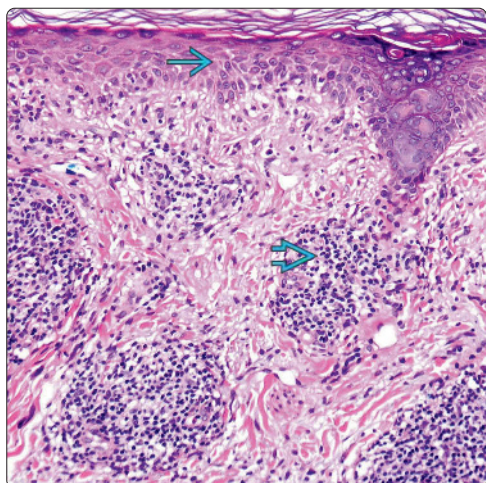


**Perifollicular Lymphohistiocytic Infiltrates**

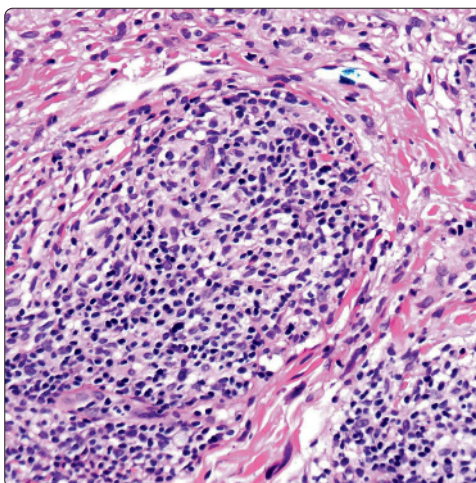


**(Left)** In this example, perifollicular granulomas with lymphocytic inflammation are present. **(Right)** Perifollicular lymphohistiocytic infiltrates are identified.

**Epidermal Spongiosis and Perifollicular Infiltrates**



**Granulomatous Inflammation**



**(Left)** Histology demonstrates epidermal spongiosis and perifollicular lymphohistiocytic aggregates with granulomas. **(Right)** High-power view of granulomatous inflammation shows a mixture of histiocytes and lymphocytes.



# Lupus Miliaris Disseminatus Faciei

## KEY FACTS

### TERMINOLOGY

- Abbreviation: Lupus miliaris disseminatus faciei (LMDF)
- Synonyms: Acne agminata, FIGURE (facial idiopathic granulomata with regressive evolution)

### ETIOLOGY/PATHOGENESIS

- Etiology is unknown at this time
  - Initially thought to be form of mycobacterial infection due to its histologic appearance of epithelioid cell granulomas with central necrosis; but has been proven noninfectious and unrelated to tuberculosis
- May represent unusual granulomatous reaction to ruptured hair follicles, possibly autoimmune response

### CLINICAL ISSUES

- Monomorphous yellowish-brown papules typically on central face with predilection for periocular areas; rarely extrafacial such as arms, axillae

### MICROSCOPIC

- Histopathologic features vary depending on stage of evolution
- Early stages show nonspecific change of nongranulomatous, perivascular, and periadnexal lymphohistiocytic infiltrate
- Mature lesions can show variety of patterns, often in association with ruptured hair follicle
  - Epithelioid cell granuloma with central necrosis (if present, diagnostic of LMDF)
  - Epithelioid cell granuloma without central necrosis (sarcoidal type granuloma)
  - Epithelioid cell granuloma with abscesses

### TOP DIFFERENTIAL DIAGNOSES

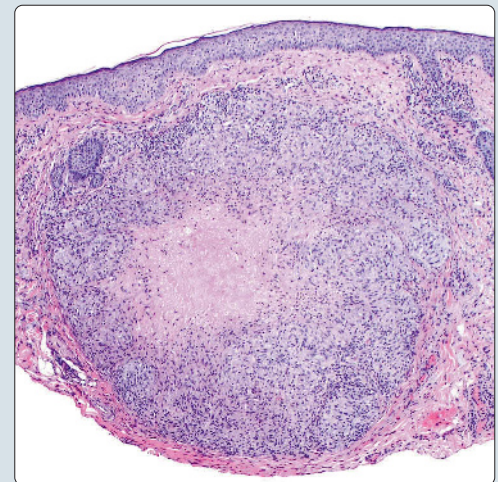
- Rosacea
- Sarcoidosis

**Lupus Miliaris Disseminatus Faciei**

(Left) This clinical image shows the typical reddish brown dome-shaped papules in periocular distribution. (Courtesy LM Bull, MD.) (Right) A mature lesion of lupus miliaris disseminatus faciei shows an epithelioid granuloma with central necrosis. (Courtesy LM Bull, MD.)

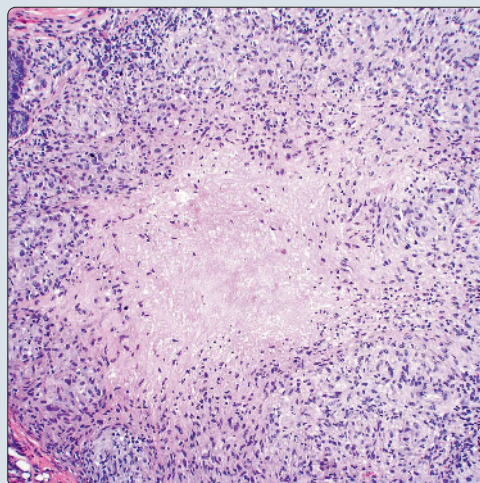


**Mature Lesion of Lupus Miliaris Disseminatus Faciei**

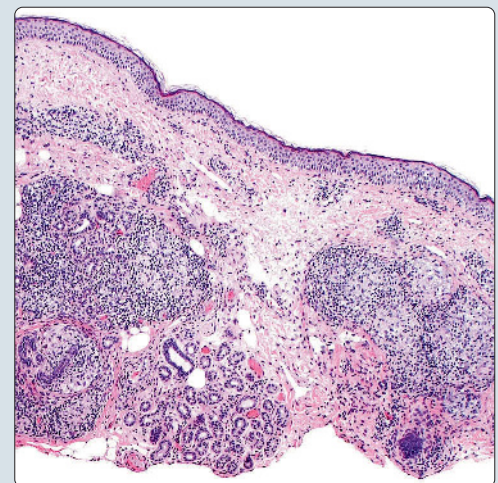


**Caseating Granuloma, Higher Power**

(Left) There is a central area of well-defined caseation necrosis surrounded by multinucleate giant cells and epithelioid cells. (Courtesy LM Bull, MD.) (Right) Early lesions can be less specific, with perivascular and perifollicular infiltrate with neutrophils, lymphocytes, or macrophages. (Courtesy LM Bull, MD.)



**Early Lesion of Lupus Miliaris Disseminatus Faciei**



## TERMINOLOGY

### Abbreviations

- Lupus miliaris disseminatus faciei (LMDF)

### Synonyms

- Acne agminata
- FIGURE (facial idiopathic granulomata with regressive evolution)
  - Proposed term to indicate that this is distinct entity separate from skin tuberculosis or granulomatous type rosacea; not yet widely accepted

## ETIOLOGY/PATHOGENESIS

### Unknown

- Initially thought to be form of mycobacterial infection due to its histologic appearance of epithelioid cell granulomas with central necrosis but has been proven noninfectious and unrelated to tuberculosis
- Some consider it form of granulomatous rosacea; however, most believe it to be separate entity based on distinct clinical presentation and absence of coexisting typical rosacea
- May represent unusual granulomatous reaction to ruptured hair follicles, possibly autoimmune response

## CLINICAL ISSUES

### Presentation

- Monomorphous yellowish-brown papules typically on central face with predilection for periorcular areas; rarely extrafacial such as arms, axillae

### Treatment

- Conventional treatment for rosacea tends to be ineffective
- Oral tetracyclines and retinoids have been tried but response is variable

### Prognosis

- Often regressive spontaneously over months to yr with some scarring

## MICROSCOPIC

### Histologic Features

- Vary depending on stage of evolution
- Early stages show nonspecific change of nongranulomatous, perivascular, and periadnexal lymphohistiocytic infiltrate
- Mature lesions can show variety of patterns
  - Epithelioid cell granuloma with central necrosis (if present, diagnostic of LMDF)
  - Epithelioid cell granuloma without central necrosis (sarcoid type granuloma)
  - Epithelioid cell granuloma with abscesses
- Often in association with ruptured hair follicle
- Not usually related to *Demodex folliculorum* as is often the case in granulomatous rosacea
- Focal vasculitis seen rarely

## ANCILLARY TESTS

### Special Stains/Culture

- AFB and Fite stains negative for *Mycobacterium tuberculosis*
- Tissue culture negative for *M. tuberculosis*

## DIFFERENTIAL DIAGNOSIS

### Rosacea

- More chronic than LMDF
  - Has exacerbating factors such as sun exposure, alcohol, and spicy food
  - No extrafacial features
  - Often associated with *Demodex* mites
- Histologic features overlap with LMDF, especially when LMDF does not show diagnostic feature of caseating granulomas

### Perioral Granulomatous Dermatitis

- Reddish brown papules and pustules in periorificial distribution
- Dermal granulomatous infiltrate without necrosis

### Facial Afro-Caribbean Eruption Syndrome

- May be variant of perioral granulomatous dermatitis; affects black Afro-Caribbean children
- Perifollicular granulomatous infiltrate without necrosis

### Sarcoidosis

- Clinical and histologic features (sarcoid type granulomas) may overlap
  - Histopathologically central necrosis not present
- However, can generally be differentiated based on physical exam, chest x-ray, and lab test (angiotensin-converting enzyme level)

### Tuberculosis

- Histopathologically can be indistinguishable
  - AFB &/or Fite positive mycobacterial organisms differentiate
  - Culture positive for mycobacterial organisms
- Clinical history should help differentiate

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## KEY FACTS

### TERMINOLOGY

- Granulomatous lesions of Crohn disease (CD) involving skin that are separated from gastrointestinal/mucosal lesions by normal tissue
- Metastatic CD is synonym

### CLINICAL ISSUES

- Rare
- Most often occurs within flexures, genitalia, or extremities
- Nonspecific clinical picture
  - Plaques, nodules, or crusts that are typically erythematous (bright red) ± ulcers &/or induration
- Can occur simultaneously or precede intestinal involvement by years

### MICROSCOPIC

- Noncaseating or sarcoidal granulomas that are typically superficial and deep in location

- Occasionally granulomas may be perivascular in location (granulomatous perivasculitis)
- Superficial and deep perivascular mixed inflammatory infiltrate
- Eosinophils typically abundant
- Often has massive edema in dermis
- Ulceration common (~ 1/2 of cases)

### TOP DIFFERENTIAL DIAGNOSES

- Sarcoidosis
- Leprosy
- Pyoderma gangrenosum (specifically superficial granulomatous pyoderma)
- Other infectious granulomatous dermatitides
- Foreign body granulomatous reaction
- Tuberculosis

### Ulcerated Papules



*Ulcerated erythematous papules are seen over the neck and upper back in a man with Crohn disease. The biopsy was compatible with metastatic Crohn disease.*

## TERMINOLOGY

### Abbreviations

- Cutaneous Crohn disease (CCD)
- Crohn disease (CD)

### Synonyms

- Metastatic CD

### Definitions

- Granulomatous lesions of CD involving skin that are separated from gastrointestinal/mucosal lesions by normal tissue

### Historical Point of Interest

- It has been suggested by some researchers that Darwin suffered from CD
  - Lactose intolerance and other conditions have also been hypothesized

## ETIOLOGY/PATHOGENESIS

### Precise Cause Unknown

- Probably combined heritable and environmental factors
  - Numerous gene loci have been shown to increase susceptibility to disease
  - End result is improper immune function with activation of T cells and chronic inflammation leading to tissue injury

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Rare
  - ~ 50 cases reported in literature
    - Probably more common, as simple case reports are now no longer novel enough to warrant publication
    - 1st described in 1965
- Age
  - More common in adults but can also occur in children

### Site

- Most often occurs within flexures, genitalia, or extremities
  - Submammary, retroauricular, abdominal skin folds, umbilicus
  - Penile, vulvar, etc.
  - Thigh, forearm, other sites also reported but more rare
- May appear anywhere on skin

### Presentation

- Nonspecific clinical picture
  - Plaques, nodules, or crusts
  - Typically erythematous (bright red) ± ulcers &/or induration
- Can occur simultaneously or precede intestinal involvement by years
  - More commonly precedes intestinal disease in children
- Cutaneous involvement is rare
  - Most commonly secondary to direct extension from GI tract to skin
    - Perianal ulceration
    - Fistulae development

- In ~ 10% of patients, perianal fistula is initial presentation of CD
  - In relation to scar after surgery
  - May occur around ileostomy or colostomy sites
  - Erythema and edema of genitalia
- Rarely occurs without contiguity of GI tract

### Laboratory Tests

- Erythrocyte sedimentation rate &/or C-reactive protein should be elevated

### Treatment

- Surgical approaches
  - Some cases show good results with surgery alone
- Drugs
  - Metronidazole, mesalamine, and prednisone
  - Azathioprine can also be used
  - Refractory cases may respond to cyclosporine, tacrolimus, or biologics
    - Infliximab, adalimumab, others

### Prognosis

- Severity of cutaneous disease does not always parallel gastrointestinal activity
  - Course can be entirely independent from gastrointestinal disease
- Treatment with drugs can yield varying degrees of success

## MICROSCOPIC

### Histologic Features

- Noncaseating or sarcoid-like granulomas that are typically superficial and deep in location
  - Occasionally, granulomas may be perivascular in location (granulomatous perivasculitis)
- Superficial and deep perivascular mixed inflammatory infiltrate
  - Eosinophils typically abundant
- Often has massive edema in dermis
- ± necrotizing granulomatous vasculitis
- Ulceration common (~ 1/2 of cases)
- Rare cases have shown lichenoid and granulomatous reaction pattern

## ANCILLARY TESTS

### Histochemistry

- Fungal stains (PAS, GMS) should always be performed on granulomatous infiltrates
  - Should be negative in CCD
- Acid-fast bacilli (AFB) &/or Fite stains should also be done in any cutaneous granulomatous infiltrate
  - Should be negative in CCD
- Polarizing microscopy reveals no foreign material

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Sarcoidosis
  - "Naked" (lymphocyte-poor) granulomas would favor sarcoidosis (CCD is typically lymphocyte rich)
  - Ulceration very uncommon
  - Eosinophils minimal or absent

- Typically no edema
- Leprosy
  - Clinical history (paresthesia), travel to endemic area should help decipher
  - Culture, serology, molecular tests, or identification of acid-fast bacilli on special stain is confirmatory
  - Granulomas in leprosy are more arciform or linear and typically follow neurovascular bundles
  - Dermal edema is typically not present
- Pyoderma gangrenosum (specifically superficial granulomatous pyoderma)
  - Can also be seen in CD
  - Can also have granulomatous inflammation with giant cells, neutrophils, and eosinophils
  - Typically has pseudoepitheliomatous hyperplasia and heavy neutrophilic infiltrate
- Other infectious granulomatous dermatitides
  - Other infections, such as atypical mycobacteria, may also be in histopathologic differential diagnosis
    - Culture or identification of infectious organisms with special stains is best way to differentiate
- Foreign body granulomatous reaction
  - Silica, zirconium, tattoo pigment, and beryllium can also cause granulomatous infiltrate at times
  - Foreign material may be evident (tattoo pigment)
  - Absence of clinical history of intestinal CD
  - History of trauma (may be remote)
  - Polarizing microscopy may reveal refractile foreign material
- Tuberculosis
  - Caseous necrosis within granulomas is hallmark
    - CCD is noncaseating
  - AFB stain, culture, Mantoux skin test, serologies, or other laboratory tests can help differentiate from CCD

## Clinical

- Cutaneous tuberculosis
  - Patient should have history of contact with infected patient
  - PPD skin test can be helpful as screening test
  - Biopsy &/or culture is most helpful in differentiating
    - Biopsy typically shows tuberculoid granulomas with areas of caseous necrosis (vs. CCD)
      - Positive staining for acid-fast bacilli in biopsy tissue is confirmatory
    - Positive culture for mycobacteria or isolation of mycobacterial DNA on PCR from tissue is gold standard
- Leprosy
  - Dull in color
  - Loss of sensation or paresthesia (especially in tuberculoid leprosy)
    - In lepromatous leprosy, sensation is preserved
  - History of travel to endemic area or contact with infected person
  - Can often see or feel enlarged nerve clinically
  - Slit-skin smear can be used for rapid diagnosis
  - PCR can be confirmatory
- Sarcoidosis
  - Cutaneous lesions rarely ulcerate (vs. CCD)
  - Apple-jelly (dull reddish-brown) coloration

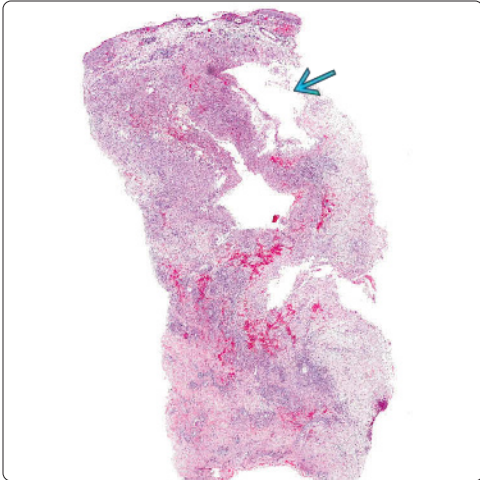
- Not bright red like CCD
- Mediastinal lymphadenopathy
- Sweet syndrome
  - Erythematous plaques
  - Larger lesions
  - Patient usually febrile
- Pyoderma gangrenosum
  - Appears very similar clinically
  - Ulcer with rolled, undermined edge
  - Always ulcerates
  - Typically large lesions
  - Very painful
- Syphilis
  - Usually painless
  - More circular and usually single
  - Indurated around edge (hard chancre)
- Polyarteritis nodosa
  - Ulcerative nodules
  - Livedo reticularis common
  - Typically on lower legs

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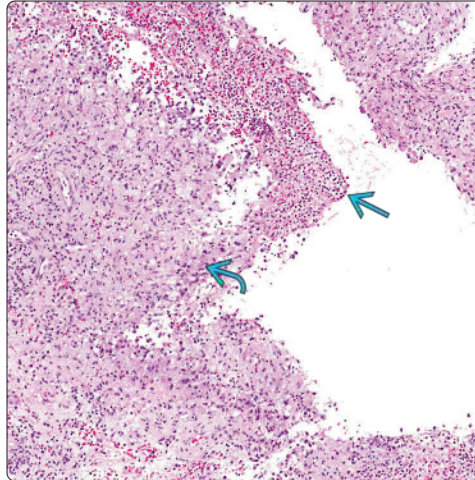
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**Superficial and Deep Granulomatous Dermatitis**

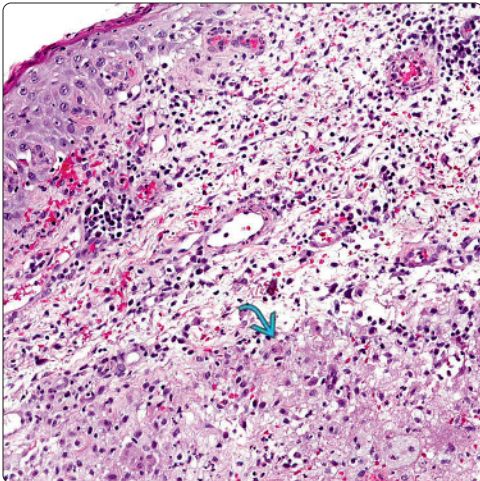


**Mixed Inflammation With Sarcoidal Granulomas**

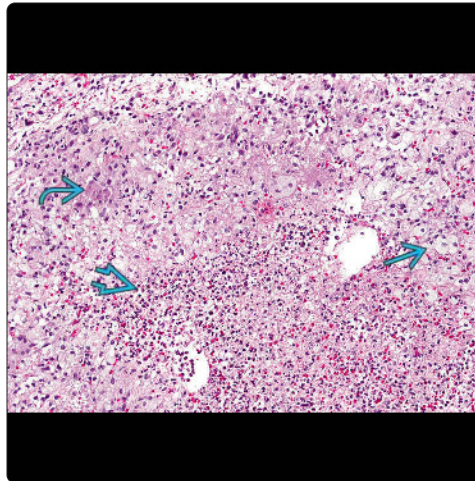


(Left) Low-power view of cutaneous Crohn disease (CCD) demonstrates a superficial and deep granulomatous dermatitis with areas of massive edema. (Right) This section shows a sarcoidal granulomatous dermatitis with mixed inflammation containing numerous neutrophils and edema.

**Sarcoidal Granulomas**

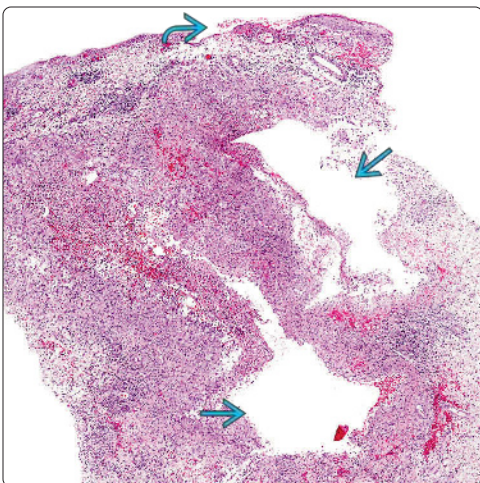


**Histiocytes Surrounding Neutrophils**

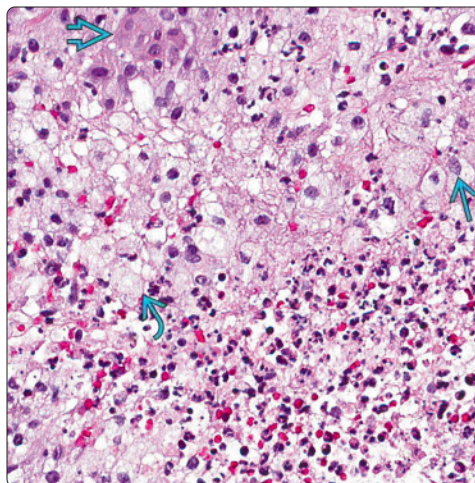


(Left) This section shows sarcoidal granulomas located very close to the epidermis with a background mixed inflammatory infiltrate. (Right) Any time you see a mixed inflammatory infiltrate composed of sarcoidal granulomas (epithelioid histiocytes) with occasional giant cells and neutrophils, special stains to rule out fungal or acid-fast bacteria are always indicated. In CCD special stains should always be negative (unless a concomitant infection is present, which would be exceedingly rare).

**Focal Ulceration With Massive Edema**



**Epithelioid Histiocytes and Giant Cells**



(Left) Medium-power view of CCD demonstrates massive dermal edema and focal cutaneous ulceration (common) as well as a superficial and deep mixed granulomatous inflammatory infiltrate. (Right) Sarcoidal granulomas are composed of epithelioid histiocytes with foamy (bubbly) cytoplasm, epithelioid nuclei, and occasionally multinucleate giant cells.



# Interstitial Granulomatous Dermatitis

## KEY FACTS

### CLINICAL ISSUES

- Interstitial granulomatous dermatitis (IGD) is subtype of reactive granulomatous dermatitis and exists along spectrum with interstitial granulomatous drug reaction (IGDR) and palisaded granulomatous dermatitis (PNGD)
- Presents as linear cords or annular erythematous plaques, usually on lateral upper trunk and proximal limbs
- Strongly associated with systemic disease (similar in regards to PNGD) such as
  - Rheumatoid arthritis, systemic lupus erythematosus, and other connective tissue disorders
  - Solid organ malignancies and hematologic malignancies
  - Rarely infections and medications

### MICROSCOPIC

- Interstitial granulomatous histiocytic dermal infiltrate with clefted, floating foci of piecemeal degenerated collagen (floating sign)

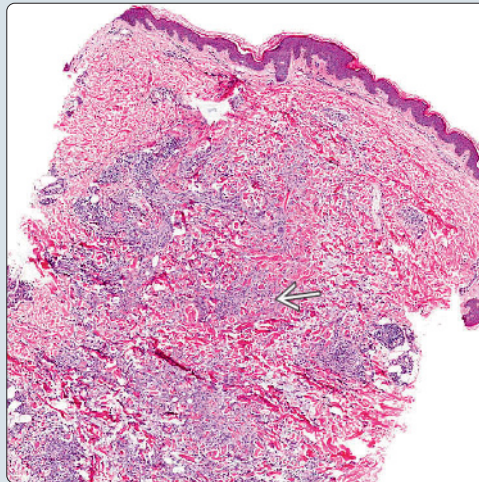
- Neutrophils or eosinophils may be seen but should not be predominant inflammatory cell
- Vasculitis should be absent (as opposed to PNGD)
- Mucin absent or minimal
- IGDR favored in cases with triad of
  - Vacuolar interface dermatitis
  - Prominent eosinophils
  - Lymphoid atypia

### TOP DIFFERENTIAL DIAGNOSES

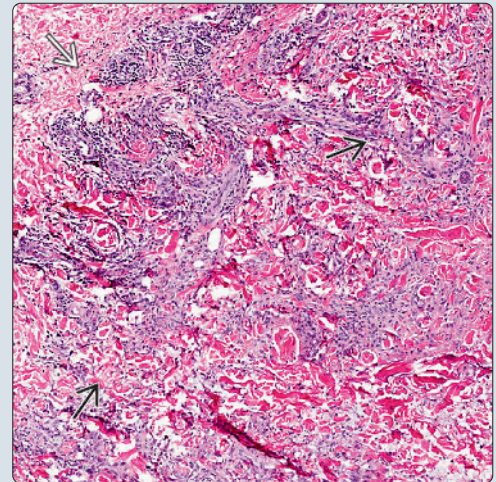
- Palisaded neutrophilic granulomatous dermatitis
- Interstitial granulomatous drug reaction
- Granuloma annulare
- Rheumatoid nodules
- Necrobiosis lipoidica
- Infection

**Low-Power Diffuse Interstitial Infiltrate**

(Left) Low-power view demonstrates a diffuse interstitial inflammatory infiltrate throughout the superficial and deep dermis [A]. (Right) Medium-power view demonstrates a diffuse interstitial inflammatory infiltrate [B] with floating, clefted collagen [C].

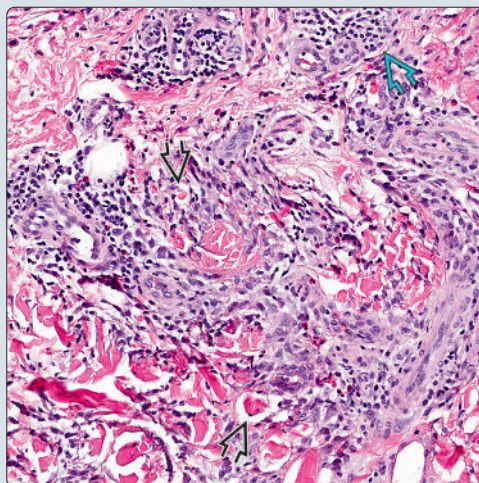


**Floating, Clefted Collagen**

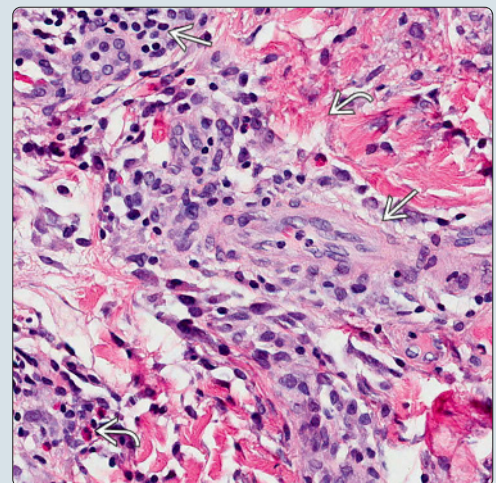


**Granulomatous Infiltrate With Degenerated Collagen**

(Left) Higher power view demonstrates an interstitial inflammatory infiltrate that is granulomatous, composed of histiocytes with admixed lymphocytes [D]. Floating degenerative collagen [E] is seen rimmed by histiocytes. Mucin is absent. (Right) Interstitial granulomatous infiltrate is composed of histiocytes and lymphocytes [F]. Eosinophils are variably present [G].



**Histiocytes, Lymphocytes, and Eosinophils**



## TERMINOLOGY

### Abbreviations

- Interstitial granulomatous dermatitis (IGD)

### Synonyms

- IGD with arthritis
- IGD with cords and arthritis
- Linear subcutaneous bands of rheumatoid arthritis
- Linear rheumatoid nodules
- Linear granuloma annulare
- Railway track dermatitis
- Ackerman syndrome

### Definitions

- IGD is subtype of reactive granulomatous dermatitis and exists along spectrum with palisaded granulomatous dermatitis (PNGD) and interstitial granulomatous drug reaction (IGDR)

## ETIOLOGY/PATHOGENESIS

### Unknown

- Poorly understood
- Thought to be similar to PNGD
- Hypothesized that chronic inflammation produces immune complex deposition in small dermal vessels resulting in inflammation, collagen degradation, and granulomatous infiltrate

## CLINICAL ISSUES

### Epidemiology

- Age
  - More common in adults but has been seen in pediatric population
- Sex
  - F:M = 3:1

### Presentation

- Linear cords or annular erythematous plaques on lateral upper trunk, buttocks, and proximal limbs
- Often firm and asymptomatic
- Strongly associated with systemic disease (similar in regards to PNGD) such as
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Other connective tissue disorders
  - Hematologic malignancies
  - Solid organ malignancies
  - Similar in this regard to PNGD
  - Rarely infections
    - Lyme disease
    - Coccidioidomycosis
  - Rarely medications

### Treatment

- Aimed at treating underlying systemic illness or removal of offending medications

## MICROSCOPIC

### Histologic Features

- Predominantly histiocytic dermal infiltrate rimming or forming rosettes of palisading histiocytes around foci of degenerated collagen
  - Inflammation tends to be deep or bottom heavy
- Floating sign
  - Clefing of histiocyte-rimmed degenerated collagen bundles
    - Present in 2/3 of cases
- Neutrophils or eosinophils may be seen but should not be predominant inflammatory cell
- Vasculitis should be absent (as opposed to PNGD)
- Mucin absent or minimal (as opposed to granuloma annulare)
- IGDR has been described as unique entity (separate from drug-induced IGD) with 3 unique pathological features
  - Vacuolar interface dermatitis with dyskeratotic keratinocytes
  - Prominent eosinophilia
  - Lymphoid atypia

## DIFFERENTIAL DIAGNOSIS

### Palisaded Neutrophilic Granulomatous Dermatitis

- More prominent neutrophilia with leukocytoclasia and leukocytoclastic vasculitis

### Interstitial Granulomatous Drug Reaction

- Vacuolar interface dermatitis
- Prominent eosinophils
- Lymphoid atypia

### Granuloma Annulare

- Infiltrate is more top heavy and patchy, less diffuse
- Mucin much more abundant

### Rheumatoid Nodules

- Larger nodules of palisading histiocytes with eosinophilic collagen degradation

### Necrobiosis Lipoidica

- Layered, broad zones of eosinophilic necrobiosis
- May have lymphocytic vasculitis
- Inflammation may extend into fat
- Plasma cells present (typically not seen in PNGD or IGD)
- Central mucin deposition

### Infection

- Numerous infections may also display nonspecific interstitial granulomatous infiltrate with neutrophils and should be ruled out with special stains &/or culture when appropriate
  - Fungal infections
  - Atypical mycobacteria
  - Leprosy

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# Palisaded Neutrophilic Granulomatous Dermatitis

## KEY FACTS

### TERMINOLOGY

- Subset of reactive granulomatous dermatitis (along with interstitial granulomatous dermatitis and interstitial granulomatous drug reaction) associated with inflammatory arthritis and other autoimmune or hematologic diseases or more rarely, medications

### ETIOLOGY/PATHOGENESIS

- Believed to be result of immune complex deposition within small dermal blood vessels leading to smoldering small vessel vasculitis, local collagen degeneration, which in turn produces palisading lymphohistiocytic response

### CLINICAL ISSUES

- Favors adults
- M < F (1:3)
- Rarely occurs without associated systemic disease
  - Includes connective tissue disease, hematologic disorders, or more rarely medications

- Skin-colored to erythematous papules, which may be umbilicated or crusted
- Favors elbows and extensor surfaces, upper extremities > lower extremities
- Lesions are generally asymptomatic but may be pruritic or mildly tender
- Focused around treating underlying associated disease or stopping causative medication

### MICROSCOPIC

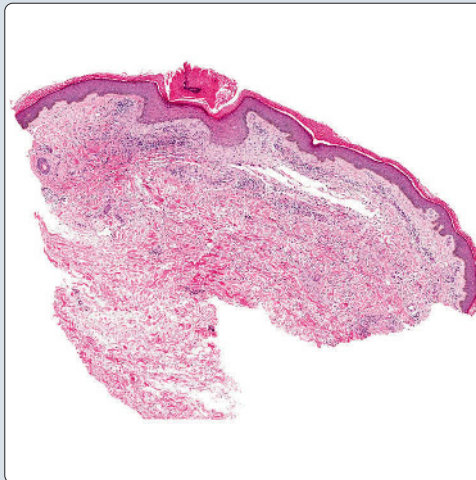
- Classic histologic findings include basophilic degenerated collagen, palisading histiocytes, neutrophils with nuclear debris ± focal leukocytoclastic vasculitis
- Features may vary with age/evolution of lesion

### TOP DIFFERENTIAL DIAGNOSES

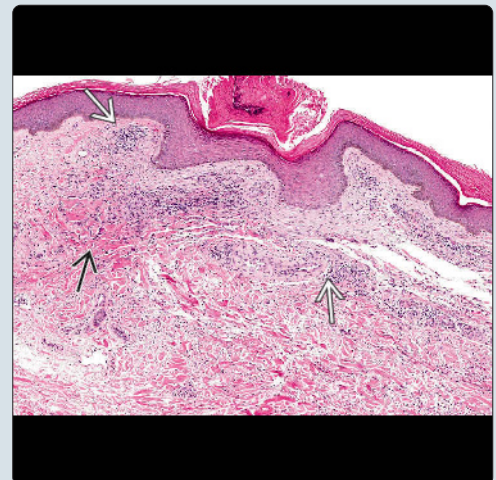
- Interstitial granulomatous dermatitis or interstitial granulomatous drug reaction
- Granuloma annulare

#### Perivascular and Interstitial Pattern

(Left) A low power view of this punch biopsy reveals a perivascular and interstitial pattern that imparts a busy look to the dermis. (Right) Granulomatous inflammation in a dermal and perivascular distribution with altered collagen typifies palisaded neutrophilic granulomatous dermatitis (PNGD).

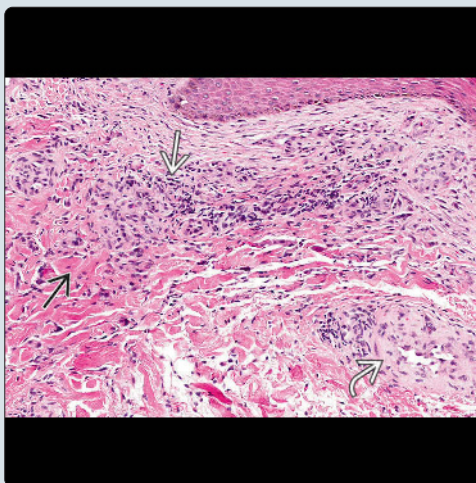


#### Perivascular Granulomatous Inflammation With Altered Collagen

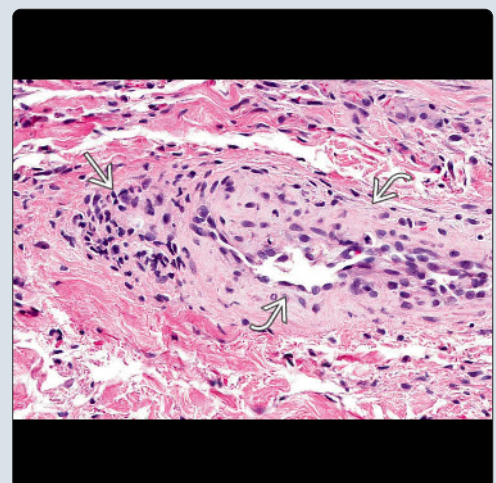


#### Altered Collagen and Endothelial Swelling

(Left) Altered collagen, endothelial swelling, and interstitial inflammation are seen in this example of PNGD. (Right) Altered dermal vessels can be seen with endothelial swelling. This well-developed lesion demonstrates less perivascular neutrophilia and karyorrhexis than would be seen in an early lesion.



#### Endothelial Swelling With Perivascular Neutrophils



## TERMINOLOGY

### Abbreviations

- Palisaded neutrophilic granulomatous dermatitis (PNGD)

### Synonyms

- Rheumatoid papules, Churg-Strauss granuloma, cutaneous extravascular necrotizing granuloma, superficial ulcerating rheumatoid necrobiosis

### Definitions

- Subset of reactive granulomatous dermatitis (along with interstitial granulomatous dermatitis and interstitial granulomatous drug reaction) associated with inflammatory arthritis and other autoimmune or hematologic diseases or more rarely, medications

## ETIOLOGY/PATHOGENESIS

### Unclear

- Believed to be result of immune complex deposition within small dermal blood vessels leading to smoldering small vessel vasculitis, local collagen degeneration, which in turn produces palisading lymphohistiocytic response

## CLINICAL ISSUES

### Epidemiology

- Age
  - Favors adults
- Sex
  - M < F (1:3)
- Associations
  - Rarely occurs without associated systemic disease
    - Rheumatoid arthritis (RA)
    - Systemic lupus erythematosus
    - antineutrophil cytoplasmic antibody vasculitis
    - Inflammatory bowel disease
    - lymphoproliferative disorders
    - Behcet
    - Other diseases
    - Medications (allopurinol, TNF inhibitors)

### Presentation

- Skin-colored to erythematous papules, which may be umbilicated or crusted
- Favors elbows and extensor surfaces, upper extremities > lower extremities
  - Trunk, head, and neck lesions present in only 1/5 of cases
- Lesions are generally asymptomatic but may be pruritic or mildly tender

### Natural History

- Waxing and waning, often self-limited over months to years

### Treatment

- Focused around treating underlying associated disease or stopping causative medication
  - Reports of treating PNGD skin lesions include intralesional vs. systemic corticosteroids or dapsone
  - Topical medications appear largely ineffective

## MICROSCOPIC

### Histologic Features

- Features may vary with age/evolution of lesion
  - Vascular changes are initially prominent follow by collagen degradation and development of palisaded histiocytes
- Earlier lesions
  - Perivascular and interstitial neutrophilic inflammation
  - Karyorrhectic debris, nuclear dust
  - Frank leukocytoclastic vasculitis in 10-30% of cases
- Later lesions
  - Basophilic piecemeal collagen degradation
  - Palisading histiocytes and small granulomas
  - ± fibrosis

## DIFFERENTIAL DIAGNOSIS

### Interstitial Granulomatous Dermatitis or Interstitial Granulomatous Drug Reaction

- Clinically, PNGD typically presents on extensor surfaces, particularly elbows and fingers whereas interstitial granulomatous dermatitis (IGD)/interstitial granulomatous drug reaction (IGDR), which favor trunk and proximal limbs
- PNGD is more likely to exhibit ulceration or crusting whereas IGD is more bland dermal process
- Histiocytic rosettes with floating sign (cleaved piecemeal degenerating collagen) without vasculitis and less prominent neutrophilic component
- IGDR is similar to IGD but with vacuolar interface dermatitis, atypical lymphocytes, prominent eosinophils

### Granuloma Annulare

- Clinically may be difficult to differentiate, but patient history of systemic disease points toward PNGD
- Ulceration or crusting also favors PNGD
- Favors top heavy patchy infiltrate with mucin
- Less intense neutrophilic infiltrate and nuclear debris

### Rheumatoid Nodule

- Often larger and deeper than PNGD lesions but given both associations with RA and extensor surfaces may be very difficult to differentiate clinically
- Central eosinophilic (not basophilic) collagen degradation
- Lesions are deeper, nodular with larger foci of necrobiosis
- Neutrophilic, cellular debris, and vasculitic component not as prominent

### Necrobiosis Lipoidica

- Clinically necrobiosis lipoidica should demonstrate orange-yellow-brown atrophy with predilection to anterior lower legs and other sites of trauma
- Layered, broad zones of eosinophilic necrobiosis
- Inflammation may extend into fat
- Plasma cells not typically seen in PNGD or IGD
- Lymphocytic > neutrophilic vasculitis
- Central mucin deposition

## SELECTED REFERENCES

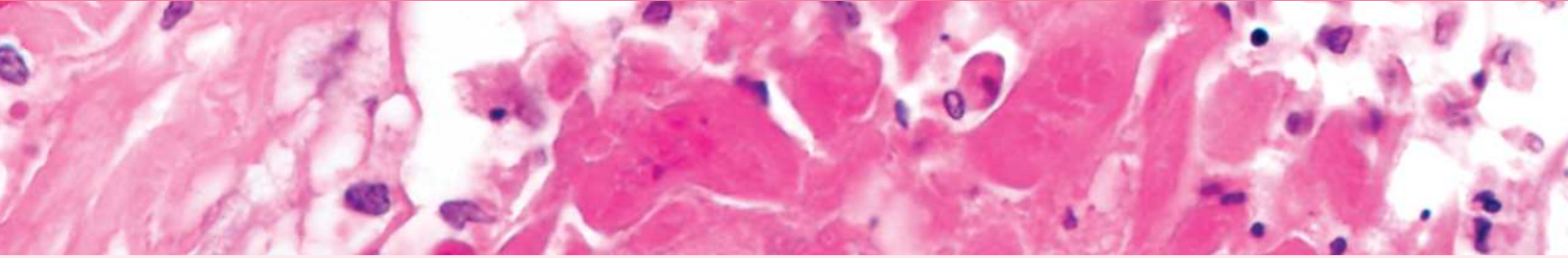
1. Rosenbach M et al: Reactive granulomatous dermatitis: a review of palisaded neutrophilic and granulomatous dermatitis, interstitial granulomatous dermatitis, interstitial granulomatous drug reaction, and a proposed reclassification. *Dermatol Clin.* 33(3):373-87, 2015

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## SECTION 11

# Pilosebaceous Diseases



Folliculitis	360
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# Folliculitis

## KEY FACTS

### TERMINOLOGY

- Folliculitis refers to infectious or noninfectious inflammation of hair follicle

### ETIOLOGY/PATHOGENESIS

- Infectious folliculitis may be bacterial, fungal, or viral; sterile folliculitis may be due to mechanical factors or induced by drugs

### CLINICAL ISSUES

- Variable presentation and distribution based on underlying cause, but often folliculocentric papules or pustules

### MICROSCOPIC

- Mixed perifollicular infiltrates, intrafollicular suppuration, and hair follicle rupture with foreign body granulomatous reaction

### ANCILLARY TESTS

- PAS, GMS, Gram stains, or immunoperoxidase for HSV-1, HSV-2, &/or VZV may be useful in excluding infectious causes

### TOP DIFFERENTIAL DIAGNOSES

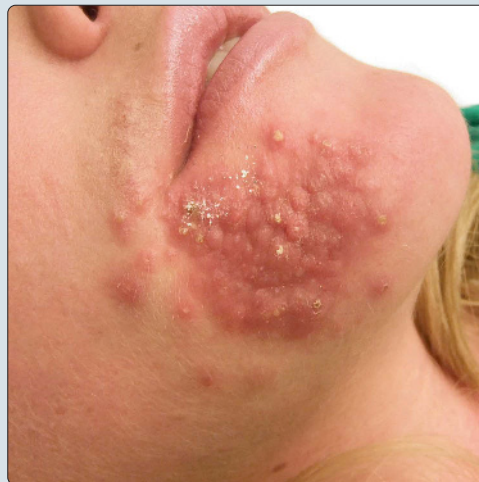
- Bacterial folliculitis
- Majocchi granuloma
- Pityrosporum* and *Demodex* folliculitis
- Herpesvirus-associated folliculitis
- Eosinophilic folliculitis

### DIAGNOSTIC CHECKLIST

- Herpesvirus-associated folliculitis may demonstrate only lymphocytic perifolliculitis and rare necrotic follicular keratinocytes

**Nodular Plaque With Pustules**

(Left) Sterile folliculitis is associated with several follicular acneiform disorders, such as pyoderma faciale, a variant of rosacea. A nodular plaque with pustules is present on the chin of a young woman. (Right) *Tinea barbae* due to *Trichophyton mentagrophytes* shows grouped pustules in the beard area of an elderly man.

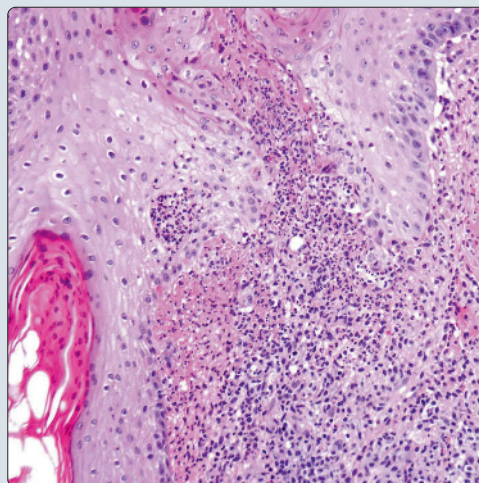


**Grouped Pustules of Tinea Barbae**

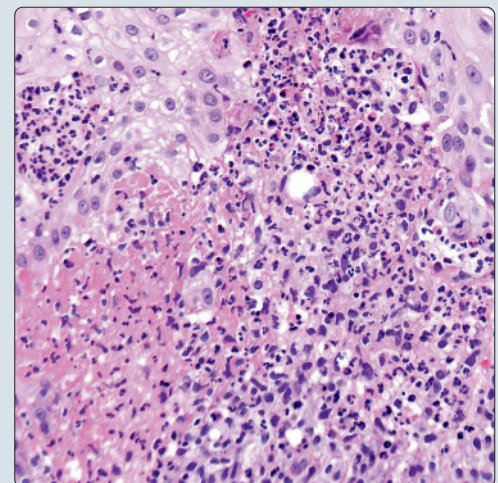


**Suppurative Inflammation Surrounding Ruptured Hair Follicle**

(Left) Ruptured suppurative folliculitis is a nonspecific histologic finding present in many acneiform processes. (Right) High-power view of ruptured suppurative folliculitis shows innumerable neutrophils surrounding a ruptured hair follicle. A granulomatous foreign body reaction is commonly associated with this histologic finding.



**Ruptured Suppurative Folliculitis**



**TERMINOLOGY****Definitions**

- Folliculitis refers to infectious or noninfectious inflammation of hair follicle

**ETIOLOGY/PATHOGENESIS****Numerous Etiologies**

- Sterile or noninfectious folliculitis is present in many inflammatory follicular acneiform disorders, but up to 1/3 of these cases demonstrate microbial colonization, most often by *Staphylococcus* species
  - Pathogenesis of sterile folliculitis is unclear but likely multifactorial, and follicular trauma and occlusion are contributory
- Eosinophilic folliculitis (EF) is of unclear etiology but occurs in both immunocompetent and immunosuppressed individuals
- Acneiform drug eruptions have been reported in association with many different agents, including corticosteroids and epidermal growth factor receptor inhibitors (EGFRIs), such as erlotinib
  - EGFRIs cause apoptosis of follicular keratinocytes, resulting in recruitment of inflammatory cytokines to pilosebaceous unit
- Causes of bacterial folliculitis include *Staphylococcus aureus* and *Pseudomonas aeruginosa*
  - *Propionibacterium acnes* is common inhabitant of pilosebaceous unit and produces inflammatory mediators in acne vulgaris following digestion of lipids
- Fungal folliculitis may be caused by dermatophytes, *Malassezia* spp., and *Candida* spp.
- Gram-negative folliculitis is due to overgrowth of *Klebsiella*, *Escherichia*, *Enterobacter*, and *Proteus* spp. following prolonged broad-spectrum antibiotic therapy
- Herpes simplex viruses (HSV) and varicella-zoster virus (VZV) may preferentially affect follicles
- Poxviruses, such as *Molluscum contagiosum* virus, may also produce folliculitis
- *Demodex* mites are found in 10% of noninflamed follicles and in over 40% of follicles with inflammation
  - However, meaning of this association is unclear, and *Demodex* may colonize inflamed follicles in conditions such as rosacea rather than cause folliculitis

**CLINICAL ISSUES****Presentation**

- Folliculitis is very common and has wide range of clinical presentations, varying by type of folliculitis as well as underlying cause
- Sterile folliculitis presents with small follicular papules or pustules over trunk, buttocks, and extremities
  - Noninfectious folliculitis is also component of disorders such as rosacea, acne vulgaris, folliculitis decalvans, and hidradenitis suppurativa, although *Demodex*, *P. acnes*, and *S. aureus*, respectively, have been associated with these disorders
- EF is divided into classic, infantile, and immunosuppression-associated subtypes

- Highly pruritic pustules, annular lesions, and urticarial plaques are common
- In classic form (Ofuji disease), lesions are distributed on face, back, and extensor arms
- In immunosuppression-associated EF, lesions predominate over face, scalp, and upper trunk
- Acneiform drug eruptions are composed of monomorphic papulopustular lesions located mainly on trunk
- Bacterial folliculitis due to *S. aureus* may present with superficial, nonscarring pustules on erythematous base, pierced by central hair
  - In contrast, deep staphylococcal folliculitis presents with painful plaques and nodules that heal with scarring; impetigo and furuncles are often associated
  - Circle of surrounding desquamation is helpful identifying feature
  - *Pseudomonas* folliculitis ("hot tub folliculitis") occurs following exposure to contaminated water
    - Characterized by pruritic or tender follicular papules or pustules on trunk
  - Gram-negative folliculitis presents with small papules and pustules around nose and mouth
- *Pityrosporum* folliculitis affects trunk and upper extremities preferentially and usually occurs in patients with history of antibiotic or corticosteroid treatment
- Majocchi granuloma is variant of tinea corporis that presents with pustular plaques on legs, often following steroid treatment
- Tinea barbae involves beard or facial hair of males
- Tinea capitis results in circumscribed patches of alopecia with scaling, erythema, broken hairs, and pustules
- Kerion is nodular variant with exuberant abscesses and crust
- Molluscum folliculitis presents with multiple umbilicated skin-colored papules in children or immunosuppressed adults
- Herpesvirus-associated folliculitis is characterized by erythema, papules and plaques, ulcers, or vesicopustules
  - Herpetic syphilis is HSV of follicles in male beard area
  - VZV may produce follicular lesions in disseminated varicella or herpes zoster

**Treatment**

- Surgical approaches
  - Neodymium:yttrium aluminum garnet (Nd:YAG) laser has been used successfully in treatment of scarring follicular acneiform disorders, such as folliculitis decalvans, hidradenitis suppurativa, and pseudofolliculitis barbae
- Drugs
  - Sterile folliculitis is treated with topical antibiotics such as benzoyl peroxide and clindamycin, systemic tetracycline class antibiotics, or isotretinoin
  - EF responds to treatment with indomethacin, steroids, isotretinoin, and, if HIV-associated, highly active antiretroviral therapy
  - Bacterial folliculitis due to *S. aureus* responds to antibiotics including mupirocin, cephalosporins, and clindamycin
    - Treatment of choice for gram-negative folliculitis is isotretinoin



- *Pseudomonas* folliculitis is self-limited and resolves without specific treatment
- o Majocchi granuloma responds to topical and oral allylamines such as terbinafine
- o Treatment of tinea capitis and tinea barbae requires systemic treatment with terbinafine or griseofulvin
- o *Pityrosporum* folliculitis responds to oral antifungal agents, particularly itraconazole
- o Herpesvirus-associated folliculitis responds to targeted antiviral treatment, including acyclovir or valacyclovir, although acyclovir resistance may occur in immunosuppressed individuals

### Prognosis

- Scarring follicular acneiform disorders, such as folliculitis decalvans, hidradenitis suppurativa, and acne keloidalis nuchae, are chronic and often refractory to treatment

## MICROSCOPIC

### Histologic Features

- In general, folliculitis demonstrates superficial and deep dermal inflammation of varying degrees around hair follicle
  - o This infiltrate may contain lymphocytes, neutrophils, or histiocytes
  - o Hair follicle rupture, with foreign body granulomatous reaction, is commonly present
  - o Acute lesions may demonstrate intrafollicular abscess or suppuration, while chronic or longstanding lesions may demonstrate surrounding granulomas or scar
- EF demonstrates perifollicular eosinophils most commonly but may also have interstitial or perivascular eosinophilic infiltrates
  - o Variable features include exocytosis of eosinophils into follicular or sebaceous epithelium, follicular mucinosis, and follicular spongiosis
- In acneiform drug eruptions, neutrophilic suppurative folliculitis with ectatic infundibula and follicle rupture is described
- Staphylococcal folliculitis often features subcorneal pustules with abscess of follicular infundibulum in superficial lesions and deeper portion of follicle and dermis in deep lesions
  - o Gram-positive cocci may sometimes be identified in follicular lumen
- *Pityrosporum* folliculitis demonstrates *Malassezia* spores within follicular infundibulum and sometimes within overlying stratum corneum
- In Majocchi granuloma, hyphae and arthrospores are identified within hair shafts and dermis, with surrounding suppuration and granulomas
- Tinea capitis and barbae show hyphae and spores inside of hair shaft (and outside, in ectothrix infection) with variable spongiosis, parakeratosis, intraepidermal and intrafollicular abscesses, and perifollicular mixed infiltrates with suppurative granulomas
- In biopsies of herpesvirus infections, folliculitis is more commonly due to VZV than HSV
  - o Most consistent findings are lymphocytic folliculitis and necrotic follicular keratinocytes
  - o Less common but helpful features include bottom-heavy infiltrates, necrosis of sebaceous lobules, and eccrine gland necrosis

- o Classic features such as multinucleated cells, ballooning degeneration, steel gray nuclei, and, in cases of herpes zoster folliculitis, epidermal surface changes are uncommon
- Molluscum folliculitis demonstrates molluscum bodies within epithelium of follicle but with sparing of interfollicular epithelium
- Depending on species of *Demodex* present, *Demodex*-associated folliculitis may show longer mites confined to infundibulum or smaller forms restricted to sebaceous epithelium

## ANCILLARY TESTS

### Histochemistry

- PAS or GMS stains are useful in identifying *Malassezia* species and dermatophytes
- Gram stain is sometimes positive in cases of bacterial folliculitis

### Immunohistochemistry

- Immunoperoxidase for HSV-1, HSV-2, &/or VZV may be helpful in cases of herpesvirus-associated folliculitis, particularly when epidermal changes are lacking or follicular changes are subtle

## DIFFERENTIAL DIAGNOSIS

### Bacterial Folliculitis

- Bacterial colonies, most often *S. Aureus*, are identified

### Majocchi Granuloma

- Dermatophyte hyphae &/or arthrospores are identified
- Step sections may be required to identify fungal elements in hair shaft, which can be missed on initial sections or fungal stains

### *Pityrosporum* and *Demodex* Folliculitis

- Cannot distinguish from colonization based on histology alone

### Herpesvirus-Associated Folliculitis

- Separated from suppurative folliculitis based on (sometimes subtle) acantholysis and cytopathic effect

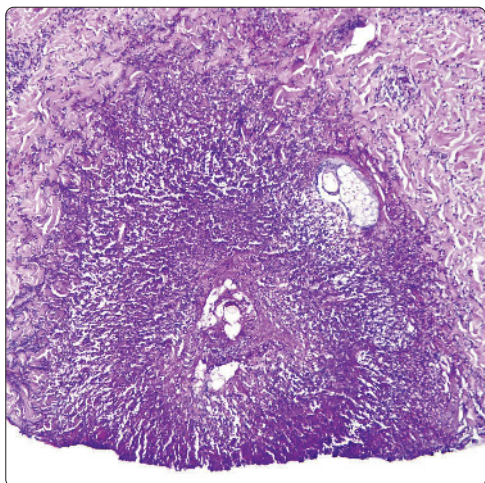
### Eosinophilic Folliculitis

- Clinicopathologic correlation may be required to distinguish from alopecia areata and follicular mucinosis

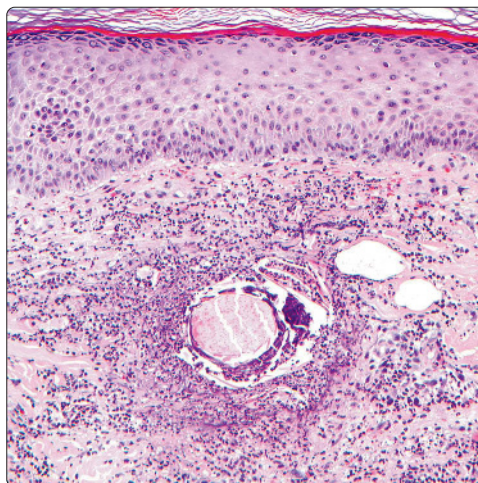
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2. Laureano AC et al: Facial bacterial infections: folliculitis. *Clin Dermatol*. 32(6):711-4, 2014
3. Lee WJ et al: Facial and extrafacial eosinophilic pustular folliculitis: a clinical and histopathological comparative study. *Br J Dermatol*. 170(5):1173-6, 2014

**Dense Neutrophilic Infiltrate Surrounding Hair Follicle**



**Neutrophils Surrounding Hair Shaft**



**(Left)** Suppurative folliculitis is characterized by a dense, neutrophilic infiltrate surrounding a follicle. **(Right)** Suppurative folliculitis characterized by a central hair shaft surrounded by neutrophils is shown. The epithelium has been destroyed by the infiltrate.

**Multiple Pustules of Bacterial Folliculitis**

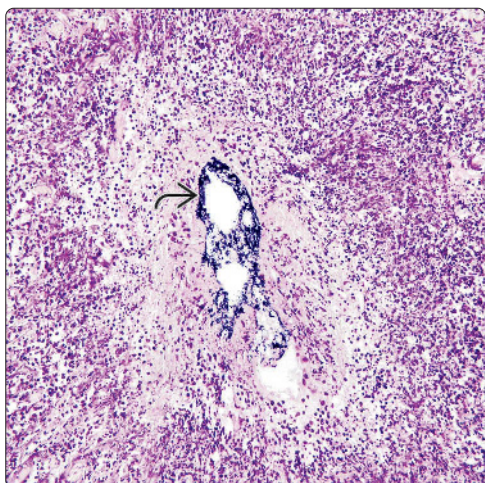


**Staphylococcal Folliculitis of Legs**

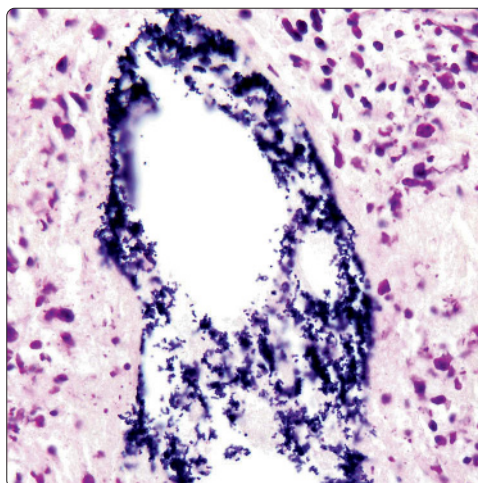


**(Left)** Bacterial folliculitis due to *Staphylococcus aureus* in a patient with severe atopic dermatitis shows multiple pustules that are present on a background of erythema, scale, and lichenification. **(Right)** Staphylococcal folliculitis of the legs is often related to shaving and requires drainage of individual follicular abscesses as well as decontamination of the surface staphylococcal carriage.

**Gram-Positive Bacteria Within Hair Canal**



**Large Clusters of Gram-Positive Cocci**



**(Left)** Brown-Hopps stain of staphylococcal folliculitis demonstrates many gram-positive bacteria within the hair canal. **(Right)** Brown-Hopps stain of staphylococcal folliculitis demonstrates large gram-positive cocci in clusters within the hair canal.



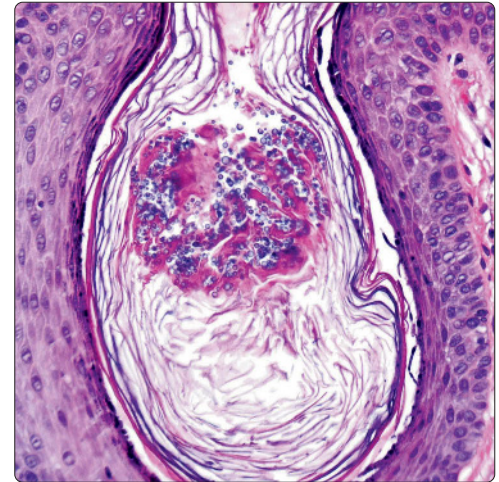
# Folliculitis

## Pruritic Follicular Pustules of "Hot Tub" Folliculitis

(Left) In "hot tub" folliculitis, the lesions are typically pruritic rather than tender. They tend to occur in covered areas (typically the trunk) after exposure to a source of contaminated water. *Pseudomonas aeruginosa* is the responsible organism. (Right) *Pityrosporum* folliculitis shows numerous *Malassezia* spores within a follicle.

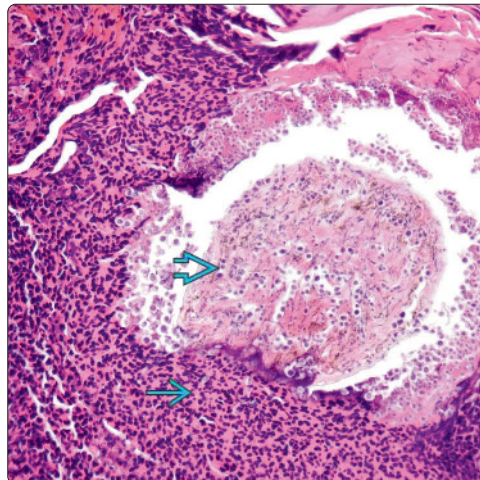


## *Pityrosporum* Folliculitis

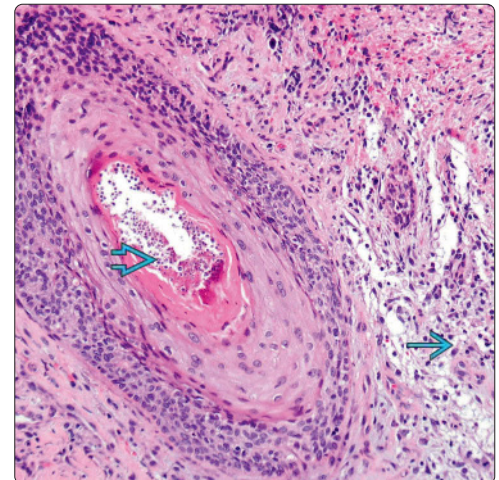


## Majocchi Granuloma With Numerous Hyphae

(Left) Majocchi granuloma shows a free hair shaft with numerous hyphae surrounded by suppuration. (Right) Majocchi granuloma is shown. Hyphal forms within a hair shaft are indicative of dermatophyte infection. Note surrounding granulomatous response.

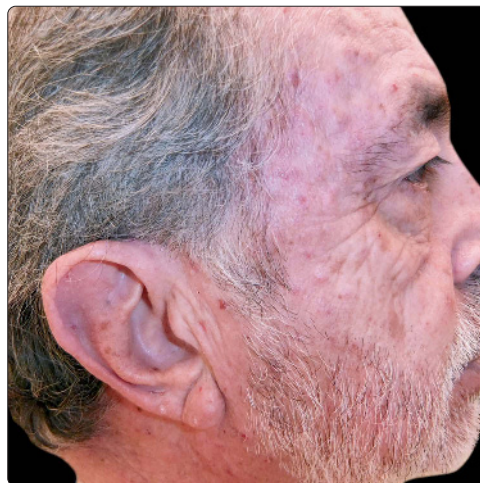


## Hyphal Forms in Hair Shaft in Majocchi Granuloma

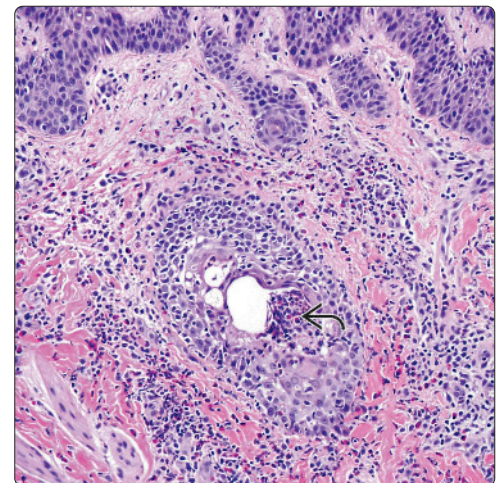


## Excoriated Vesicles of Eosinophilic Folliculitis

(Left) Immunosuppression-associated eosinophilic folliculitis shows numerous excoriated vesicles over the head and neck of an elderly man with leukemia. (Right) Eosinophilic pustular folliculitis demonstrates numerous eosinophils surrounding and infiltrating a hair follicle.

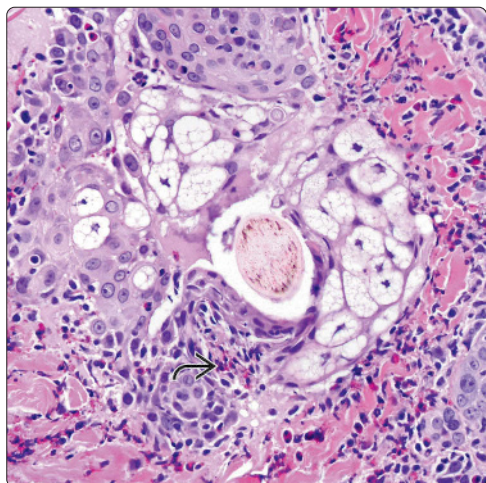


## Numerous Eosinophils Surrounding Hair Follicle

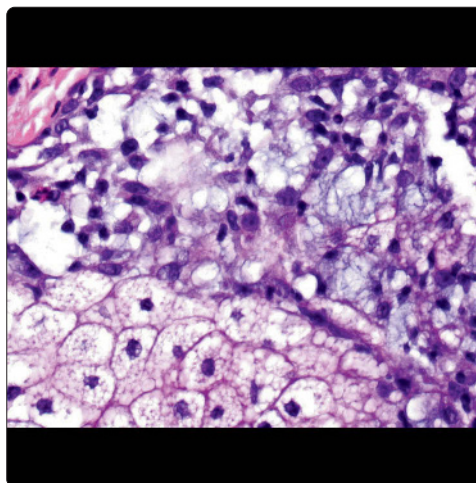




**Numerous Eosinophils of Eosinophilic Pustular Folliculitis**

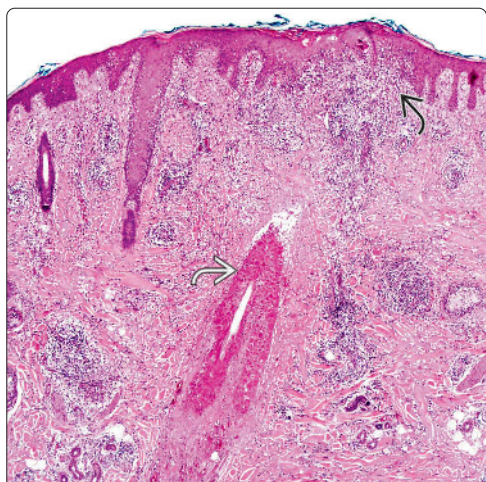


**Mucin, High-Power View**

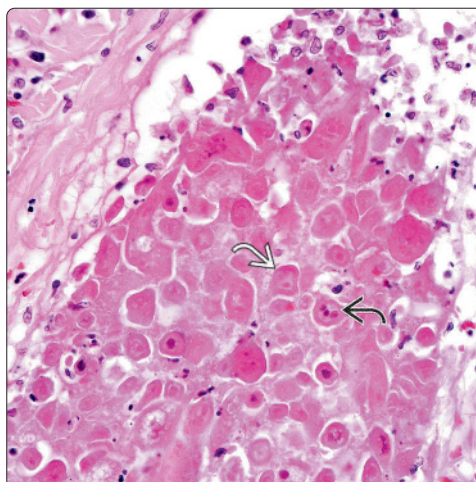


(Left) High-power view of eosinophilic pustular folliculitis demonstrates numerous eosinophils disrupting the follicular apparatus. (Right) Mucin is also commonly identified within the folliculosebaceous unit in eosinophilic pustular folliculitis.

**Inflammatory Infiltrate Overlying Hair Follicle**

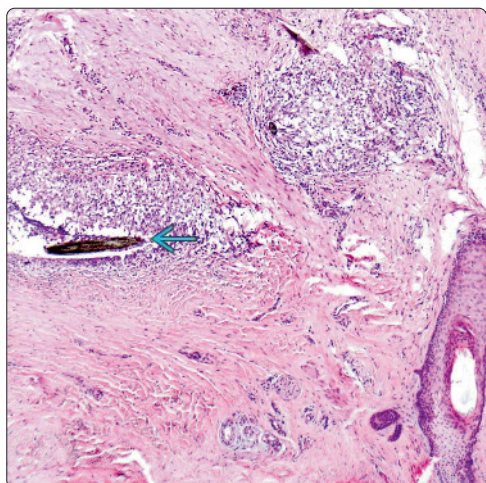


**Herpes Folliculitis With Multinucleation and Chromatin Margination**

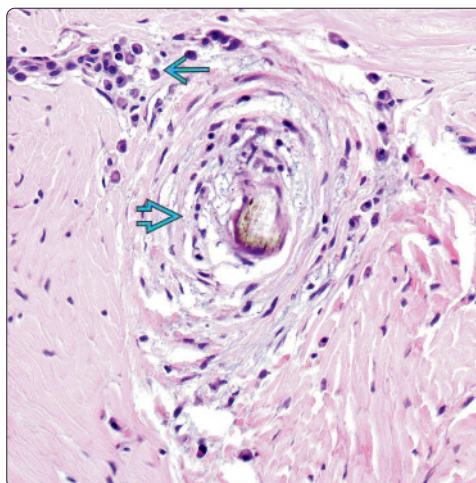


(Left) Low-power view of herpes folliculitis shows a hair shaft that, on higher power, showed classic changes associated with HSV infection. There is an overlying inflammatory infiltrate involving the epidermis. (Right) High-power view shows a hair shaft involved by herpes infection. Note the characteristic features of multinucleation and margination of chromatin.

**Free Hair Shafts With Suppuration in Acne Keloidalis Nuchae**



**Free Hair Shaft With Fibrosis**



(Left) Acne keloidalis nuchae is shown. This is a chronic folliculitis that results in scarring alopecia. Note free hair shafts surrounded by suppuration and granulomatous foreign body reaction. (Right) Free hair shaft surrounded by fibrosis and plasmacellular infiltrate is shown.



## KEY FACTS

## TERMINOLOGY

- Chronic sebaceous follicle-based inflammatory disease of uncertain etiology

## ETIOLOGY/PATHOGENESIS

- Multifactorial including genetic factors, infection with *Propionibacterium acnes*, environmental factors, and diet

## CLINICAL ISSUES

- Occurs mainly in adolescents
- No gender predilection
  - Usually more severe in males
- Single or grouped comedones, inflamed papules, pustules, nodules, cyst-like lesions, &/or scars
- Predominantly on face, back, shoulders, neck, and chest
- Treat early and vigilantly if scarring is anticipated
- Notable variants
  - Acne rosacea, acne conglobata, acne keloidalis nuchae, chalazion, follicular occlusion triad

## MICROSCOPIC

- Follicular dilatation
- Round to oval collections of laminated keratin, sebum, and bacteria
- Surrounding perifollicular inflammatory infiltrate
- Neutrophils, lymphocytes, and histiocytes
- Variable scarring

## TOP DIFFERENTIAL DIAGNOSES

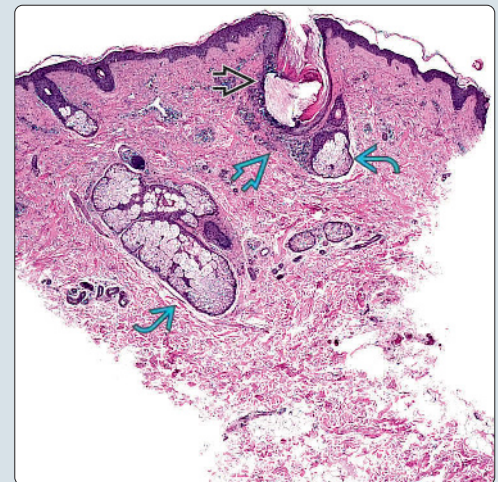
- Histological
  - Folliculitis
  - Hidradenitis suppurativa
  - Fungal infection
  - Mycobacterial infection
- Clinical
  - Epidermal cyst
  - Milia
  - Keratosis pilaris

## Comedones, Papules, Nodules, and Scars

(Left) Displayed are all types of acne lesions: Comedones [A], inflamed papules [B], pustules [C], inflamed nodules [D], and scars [E]. (Right) In this punch biopsy of an inflamed comedo, there is a dilated follicle [A] with associated sebaceous glands [B] and inflammatory infiltrate [C].

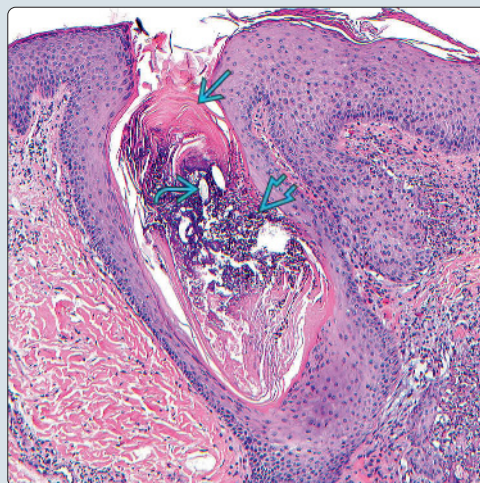


## Inflamed Comedone

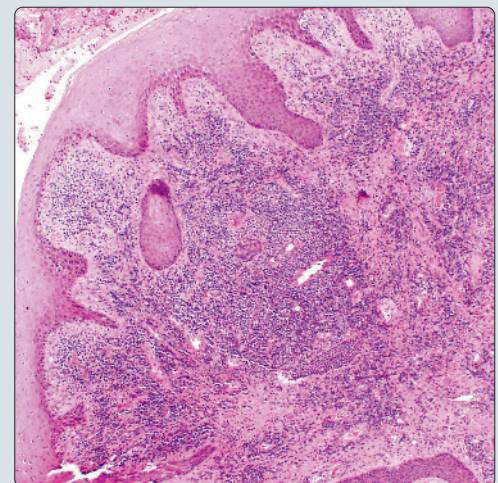


## Inflamed Comedone Filled With Keratin

(Left) An inflamed comedone is shown. The hair follicle is filled by laminated keratin layers [A], acute inflammation [B], and a central hair follicle [C]. (Right) The surrounding dermis is filled with an inflammatory infiltrate composed of neutrophils, lymphocytes, plasma cells, and occasional histiocytes.



## Adjacent Mixed Infiltrate



**TERMINOLOGY****Abbreviations**

- Acne vulgaris (AV)

**Definitions**

- Chronic sebaceous follicle-based inflammatory disease of uncertain etiology
  - Numerous variants

**ETIOLOGY/PATHOGENESIS****Environmental Exposure**

- Aerosolized oils (such as in gas stations), occlusive topical preparations, halogenated compounds (bromides, iodides, chlorides, fluorides), certain foods, and some medications

**Infectious Agents**

- *Propionibacterium acnes*

**Other**

- Hyperandrogenism: Both physiological and pathological
- Genetic
- Low apolipoprotein A1 serum levels

**CLINICAL ISSUES****Epidemiology**

- Age
  - Occurs mainly in adolescents
    - May happen in infants and middle-aged adults
- Sex
  - M = F
    - Usually more severe in males
- Ethnicity
  - Occurs in all ethnic groups

**Site**

- Predominantly on face, back, shoulders, neck, and chest

**Presentation**

- Single or grouped comedones, inflamed papules, pustules, nodules, cyst-like lesions, &/or scars

**Treatment**

- Drugs
  - Topical and oral options
    - Antibiotics, keratinolytics, retinoids, hormonal therapy
  - Intralesional corticosteroids
- Lasers and photodynamic therapy
- Dietary modifications, change of environmental surroundings

**Notable Variants**

- Acne rosacea
  - Macular erythema of face with acneiform papules
  - Usually at least a few comedones
  - Granulomatous and lymphocytic perifollicular inflammation
- Acne conglobata
  - Nodulocystic acne of face and trunk
- Acne keloidalis nuchae

- Keloid-like scarring on posterior neck at base of scalp, most commonly in black males
- Hair shafts in dermis with histiocytes, plasma cells, lymphocytes, and multinucleated giant cells
- Chalazion
  - Erythematous nodule of inner eyelid
  - Granulomatous inflammation involving meibomian sebaceous gland
- Follicular occlusion triad
  - Acne conglobata, folliculitis decalvans, and hidradenitis suppurativa
- Drug-induced acneiform eruption
  - Most commonly due to steroids, lithium, phenytoin, and iodides
- Chloracne
  - Almost entirely comedones
  - Associated with oil or chemical exposure

**MICROSCOPIC****Histologic Features**

- Follicular dilatation
- Round to oval collections of laminated keratin, sebum, and bacteria
- Surrounding perifollicular inflammatory infiltrate
- Neutrophils, lymphocytes, and histiocytes
- Variable scarring

**DIFFERENTIAL DIAGNOSIS****Histological**

- Folliculitis
  - No comedones
  - Acute &/or chronic inflammation in and around hair follicles
  - Organisms may be present within hair follicle
- Hidradenitis suppurativa
  - Ruptured follicles with chronic and granulomatous inflammation
  - Sinus tracts
- Fungal infection
  - GMS or PAS (+) organisms within granulomatous areas
- Mycobacterial infection
  - AFB &/or Fite (+) organisms within granulomatous areas

**Clinical**

- Epidermal cyst
  - Keratin-filled cyst without bacteria
  - Usually no inflammation unless ruptured
- Milia
  - Usually no associated sebaceous gland or dilated follicle
  - No bacterial colonization
- Keratosis pilaris
  - Spiny keratin plug protruding from follicular infundibulum


**SELECTED REFERENCES**

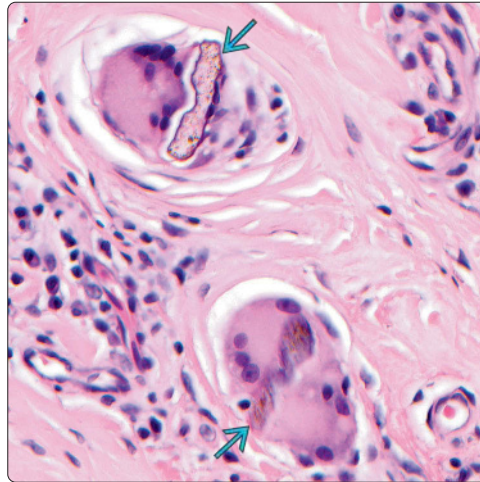
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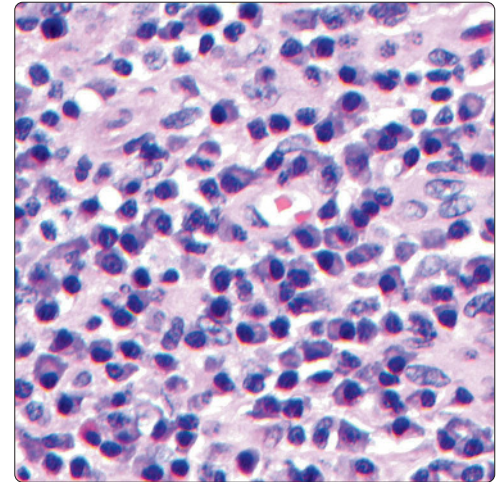
# Acne

## Hair Shafts in Giant Cells


**(Left)** *Acne keloidalis nuchae* (AKN) is also characterized by the presence of hair shafts  within multinucleated giant cells. There is an abundant chronic inflammatory infiltrate throughout the dermis consisting of lymphocytes and plasma cells. **(Right)** In AKN, there is a prominent plasma cell infiltrate with a few background lymphocytes.

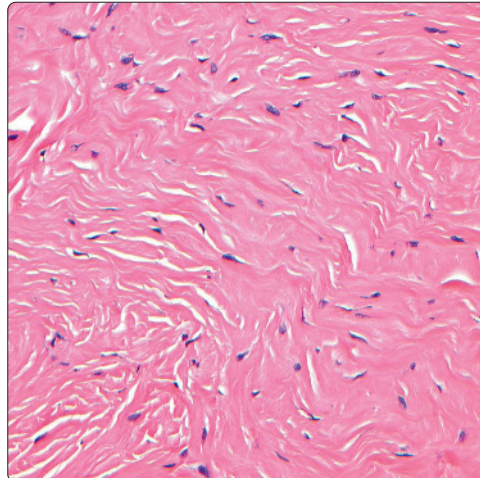


## Plasma Cell Infiltrate in Acne Keloidalis Nuchae

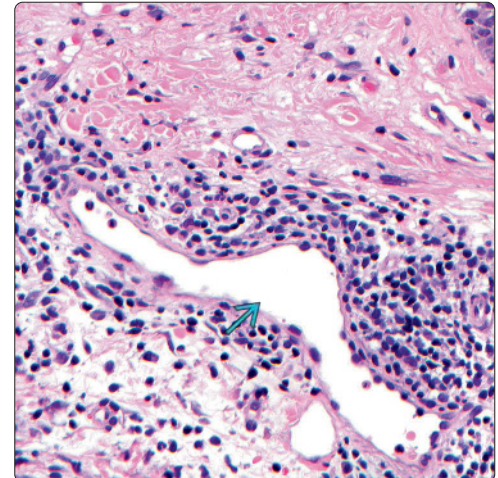


## Late-Stage Scarring in Acne Keloidalis Nuchae




**(Left)** As AKN progresses, there is prominent collagen fiber deposition with low cellularity. The chronic inflammatory infiltrate has disappeared, and there are no hair shafts remaining in this portion of the dermis. **(Right)** Acne rosacea is characterized by the presence of ectatic blood vessels  and surrounding chronic inflammation adjacent to hair follicles.

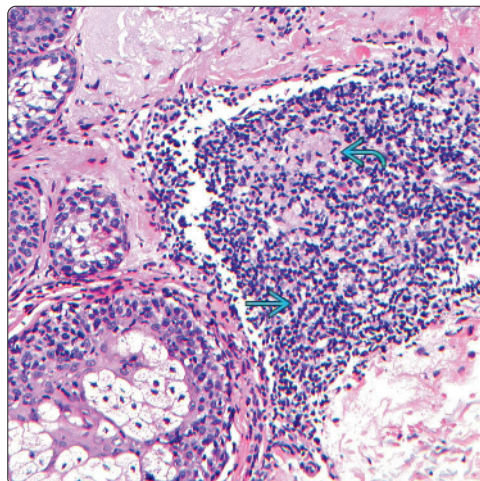


## Acne Rosacea

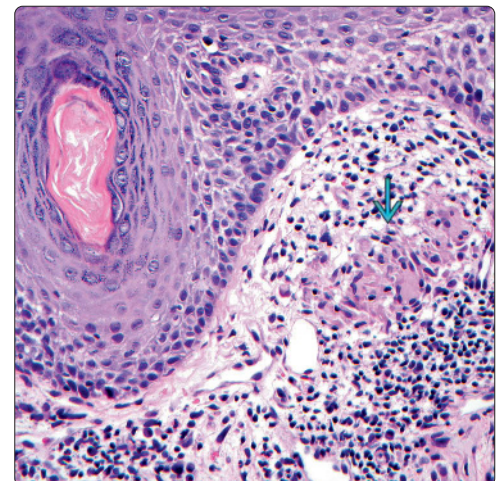


## Lymphocytes and Histiocytes

**(Left)** Adjacent to the sebaceous gland of this hair follicle is prominent chronic inflammation  with admixed histiocytes . This is characteristic of acne rosacea. **(Right)** Acne rosacea may also have more tuberculoid-type granulomas  with multinucleated giant cells. Especially in these cases, fungal or mycobacterial infection should be excluded.

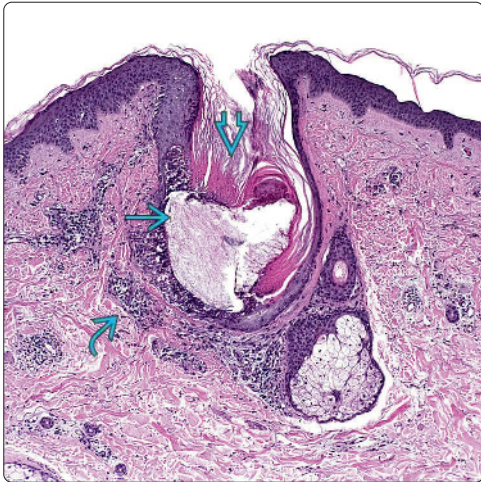


## Granulomas

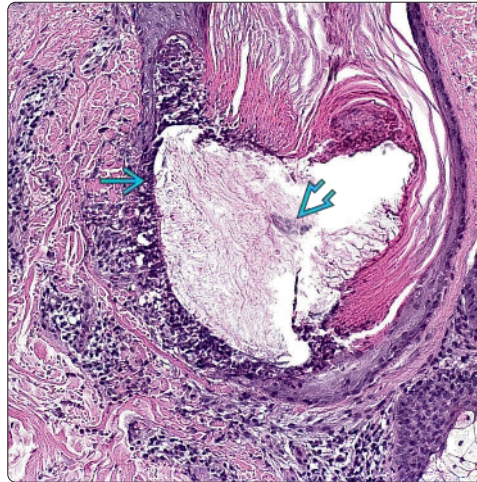




**Acne Vulgaris**

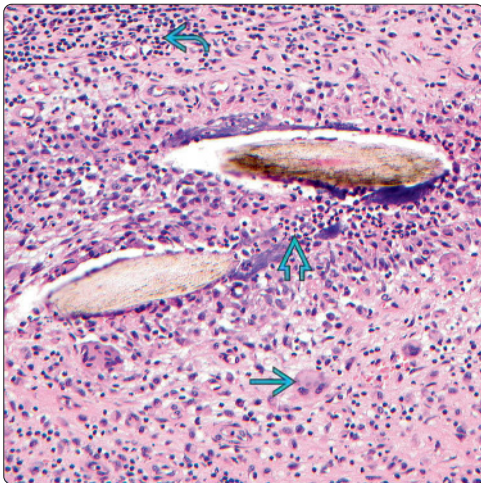


**Thinning of Hair Follicle Wall**

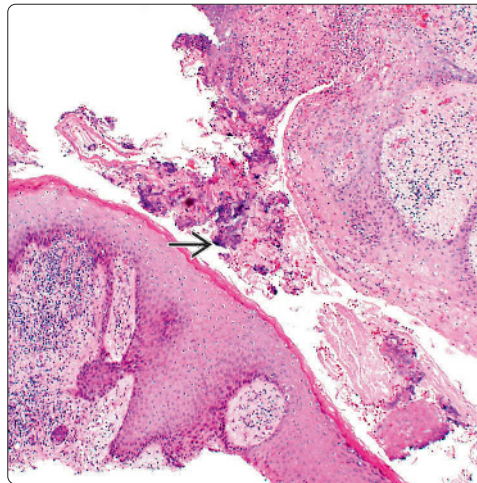


(Left) Acne vulgaris (AV) has follicular dilatation with a collection of laminated keratin and sebum. There is a surrounding mixed inflammatory infiltrate consisting of neutrophils, lymphocytes, and histiocytes. (Right) Close-up reveals thinning of the follicular wall and its permeation with the inflammatory infiltrate as well as the collection of bacteria in the center of the follicle (blue hazy material).

**Naked Hair Shafts**

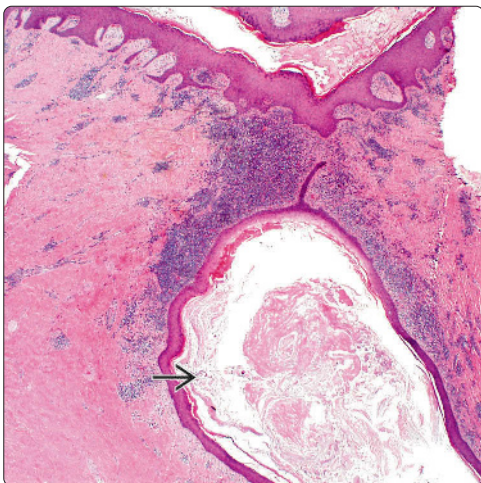


**Acne Conglobata**

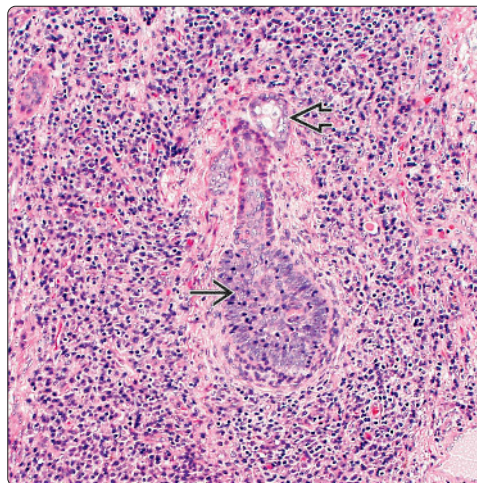


(Left) It is common in cases of AV to have liberated hair shafts in the dermis. The hair shafts are surrounded by neutrophils, lymphocytes, histiocytes, and multinucleated giant cells. (Right) Acne conglobata is characterized by multiple comedones, inflamed nodules, and cysts on the face. Here, a hair follicle has abundant keratin and bacteria occluding the follicular ostium.

**Cysts in Acne Conglobata**



**Abundant Inflammation**



(Left) One of the components of acne conglobata is cyst formation with surrounding chronic inflammation. At first glance, milia and epidermal cysts may have somewhat similar appearances. (Right) There is abundant chronic inflammation surrounding hair follicle. This inflammation leads to erythema and eventual scarring of the dermis. A small portion of a sebaceous gland is present, consistent with an acneiform lesion.



# Rosacea

## KEY FACTS

### TERMINOLOGY

- Rosacea is also known as acne rosacea

### ETIOLOGY/PATHOGENESIS

- Has been associated with several factors, though mechanistic theory has not been elucidated
  - Vascular abnormalities
  - Sun exposure
  - Demodex* infestation
- Different subtypes of rosacea may be due to different combinations of factors at play

### CLINICAL ISSUES

- Epidemiology
  - Onset usually between 30-50 years
  - Predominantly affects light-skinned individuals, especially those of Celtic heritage
- Presentation: 4 subtypes that may coexist

- Erythematotelangiectatic rosacea (ETR): Flushing, telangiectasias, irritable skin with burning or stinging
- Papulopustular rosacea (PPR): Erythematous papules that may be topped by pustules
- Phymatous rosacea (PhR): Thickened skin with nodularity classically affecting nose (rhinophyma)
- Ocular rosacea: Telangiectasias, erythema, scaling of lid margins
- All 4 subtypes feature central facial erythema

### MICROSCOPIC

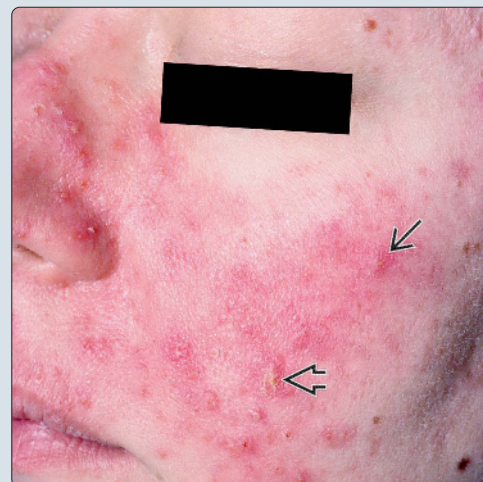
- ETR: Dilated vessels, mild edema
- PPR: Perifollicular and perivascular lymphohistiocytic infiltrate, intrafollicular neutrophils, edema
- PhR: Sebaceous gland hyperplasia, elastosis, diffuse expansion of connective tissue

### Persistent Facial Erythema and Telangiectasias

(Left) Erythrotelangiectatic rosacea is characterized by persistent facial erythema and telangiectasias. A few papules may be present, but the overall picture is erythrotelangiectatic. (Right) Papulopustular rosacea is characterized by erythematous papules that may be topped by pustules. There is also marked skin edema, which causes skin to feel hard or solid.



### Erythematous Papules

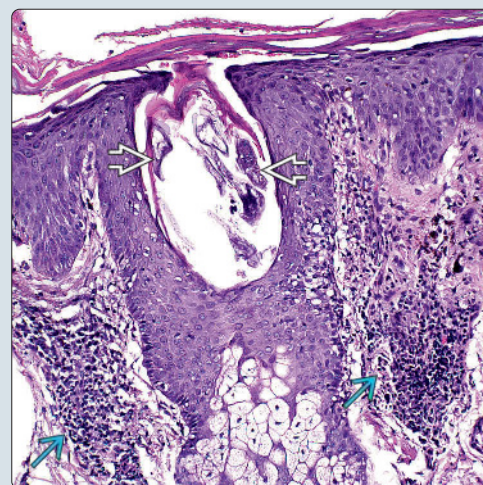


### Sebaceous Hyperplasia

(Left) This low-power view of facial skin shows sebaceous hyperplasia, as the concentration of sebaceous glands is higher than in others. (Right) Medium-power view of this skin biopsy demonstrates dense superficial to middermal perifollicular lymphohistiocytic inflammatory infiltrates. Inflammation is present adjacent to and around the hair follicle. The hair follicle is plugged, and there are *Demodex folliculorum* mite parts in the follicle.



### Perifollicular Lymphohistiocytic Infiltrate





**TERMINOLOGY****Abbreviations**

- Erythematotelangiectatic rosacea (ETR)
- Papulopustular rosacea (PPR)
- Phymatous rosacea (PhR)

**Synonyms**

- Rosacea: Acne rosacea, "curse of the Celts"
- PPR: Classic rosacea, pink papular rosacea, typologic center disease

**Definitions**

- Central facial erythema persisting for at least 3 months and may be associated with other findings
  - Facial telangiectasias, papules, pustules, flushing, burning, or stinging, and edema may be seen
  - Plaques, dryness, phymatous changes, and ocular involvement also encountered

**ETIOLOGY/PATHOGENESIS****General**

- Rosacea has been associated with several factors, but central mechanistic theory involving these factors has not been elucidated
- Different nosologic subtypes of rosacea may be due to different combinations of factors at play

**Vascular Abnormalities**

- More numerous and larger blood vessels in face compared with normal subjects
- Lack of increased cerebral blood flow from face to brain in setting of increased temperature
- Increased sensitivity to normal stimulators of flushing
- Flushing to greater degree and for longer duration compared with unaffected subjects

**Sun Damage**

- Sun damage to dermal matrix leads to pooling of serum, mediators of inflammation, and metabolic waste in skin, causing further damage
- More common in fair-skinned individuals
- Affects sun-exposed areas of face, such as cheeks and nose, with sparing of sun-protected regions, such as under chin and around eyes

**Demodex Mite Skin Infestation**

- Areas most often affected by rosacea, such as nose and cheeks, are also preferred by *Demodex*
- Tends to appear in adults, who normally have greater density of *Demodex* in skin than children
- *Demodex*-specific antibodies present in some patients

**CLINICAL ISSUES****Epidemiology**

- Incidence
  - Prevalence of 1.5% or 10.0%, per 2 European studies
  - Mild disease most common, with most affected persons having only facial erythema
- Age
  - Onset usually between ages 30-50 years

- Sex
  - Women affected almost 3x more often than men
  - Men have PhR more than women
- Ethnicity
  - Predilection for fair-skinned individuals, especially those of Celtic ancestry

**Presentation**

- 4 clinical subtypes of rosacea are generally recognized
  - Each subtype graded 1-3 based on severity
- All subtypes demonstrate gradual onset of persistent erythema of central face for at least 3 months with possible additional symptoms that characterize particular rosacea subtype
  - ETR
    - Flushing, which is more often and longer lasting than normal (10 minutes instead of few seconds to few minutes in others)
    - Telangiectasias
    - Easily irritated facial skin
    - Stinging or burning of facial skin
    - May coexist with ocular rosacea or, less frequently, PhR
  - PPR
    - Dome-shaped erythematous papules that may be topped by pustules
    - Skin edema present, which causes skin to be hard
    - Flushing and telangiectasias may be present but often less severe than ETR
    - May occur concurrently with ocular &/or PhR
  - PhR
    - Thickened skin with prominence of pores
    - Phymatous changes affect nose (rhinophyma is most common change), chin, forehead, ears, and eyelids, causing nodular facial contours
  - Ocular rosacea
    - Foreign body sensation in eye
    - Telangiectasias, erythema, scaling of lid margins
    - Conjunctivitis or blepharitis
    - Recurrent chalazions or hordeolums
    - Less frequently, sight-threatening keratitis, episcleritis, scleritis, or iritis
    - May precede, occur simultaneously, or follow cutaneous manifestations
    - Occurs in majority of rosacea patients, but often not identified if mild

**Treatment**

- ETR
  - Behavior modification to avoid stimuli causing erythema, flushing, and skin irritation
  - Topical drugs for PPR contraindicated, as these may cause irritation
  - Ablation of telangiectasias in grades 2 and 3 disease is often undertaken
- PPR
  - Topical medications for grades 1 and 2 disease; systemic for grade 3

- Medications shown to improve symptoms are tretinoin, azelaic acid, sodium sulfacetamide, and some antibacterials (metronidazole, oxytetracycline, doxycycline, minocycline, and erythromycin)
- PhR
  - Treat skin inflammation similarly to PPR, but this may not be effective
  - Surgical excision of nodules in grade 3 disease and laser ablation of telangiectasias for cosmetic reasons in grades 1 and 2 disease
- Ocular rosacea
  - Treat with topical agents (same as those used in PPR) in grade 1 disease; systemic for grades 2 and 3
  - Oral tetracycline antibiotics also helpful
  - Refer to ophthalmology if grades 2 or 3 disease present or if grade 1 persists after treatment

### Prognosis

- Chronic, relapsing, and remitting course
- Variable course that does not necessarily progress to more severe disease
- If progression occurs, follows order of ETR (least severe) to PPR to PhR (most severe)
- Increased susceptibility to solar elastosis

## MACROSCOPIC

### General Features

- Any combination of erythema, telangiectasias, papules and pustules, phymatous changes, edema, dryness, conjunctivitis, or blepharitis

## MICROSCOPIC

### Histologic Features

- ETR
  - Dilated venules and lymphatics
  - Mild edema due to chronic mild dermatitis attributable to increased irritability of skin
  - Thickening of epidermis correlating with scale at macroscopic level
  - Solar elastosis seen as increased curled, thickened elastic fibers, and hyperplasia of elastic tissue
- PPR
  - Abundant lymphohistiocytic infiltration of perivascular and perifollicular areas
  - Neutrophil collections inside follicles, corresponding to pustules macroscopically
  - Dilated and thickened veins
  - Solar elastosis is more advanced than in ETR
  - Edema corresponds to dermatitis
- PhR
  - Diffuse expansion of connective tissue, corresponding to thickened skin clinically
  - Hyperplasia of sebaceous glands with long, distorted canals and large, irregular acini
  - Epithelialized tunnels filled with inflammatory debris undermining hyperplastic sebaceous glands
  - More severe elastosis compared with ETR and PPR, with amorphous masses of degenerated elastic tissue

## ANCILLARY TESTS

### Allergy Testing

- Indicated for those with facial itching, to differentiate from allergic contact dermatitis and atopic dermatitis
- Irritable facial skin in rosacea usually manifests as stinging or burning when certain substances are applied to skin but may also manifest as itching

### Phototesting

- Indicated for those complaining of increased photosensitivity in face, to differentiate from allergic or toxic photosensitivity

## DIFFERENTIAL DIAGNOSIS

### Acne Vulgaris

- Comedones and cysts present
- No telangiectasias

### Perioral Dermatitis

- Perioral, periocular, and nasolabial folds affected
- May have history of recent topical steroid use

### Seborrheic Dermatitis

- Presents as papulosquamous dermatitis
- Usually extrafacial areas are involved
- Often coexists with and associated with rosacea

### Photosensitivity

- Presents as eczema
- Usually also involves extrafacial photoexposed areas

### Chronic Actinic Damage

- Flushing, burning, and stinging, but telangiectasias, papules, and pustules are not present

### Lupus Erythematosus (Systemic and Discoid)

- Discoid lupus erythematosus usually involves pigmentary changes, atrophy, and scarring, all of which are absent in rosacea
- Differentiation from rosacea is often complicated by fact that lupus antibodies are often present in facial skin of rosacea patients
- Histology shows vacuolar interface dermatitis, basement membrane thickening, follicular plugging, and superficial and deep perivascular and periadnexal chronic inflammation

### Atopic Dermatitis and Contact Dermatitis

- Allergy patch testing will be positive on extrafacial regions but negative in rosacea
- Contact dermatitis shows prominent spongiosis

### Carcinoid Tumor

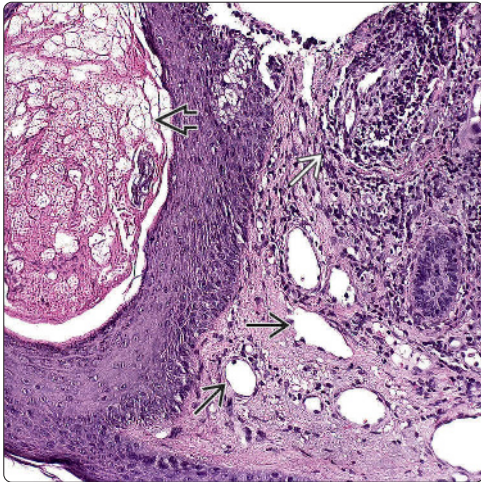
- Urine 5-HIAA will be positive in carcinoid patients but negative in rosacea

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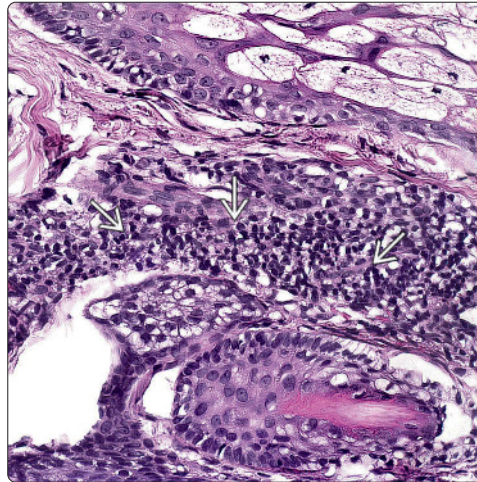
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**Follicular Plugging and Perifollicular Lymphocytic Infiltrate**

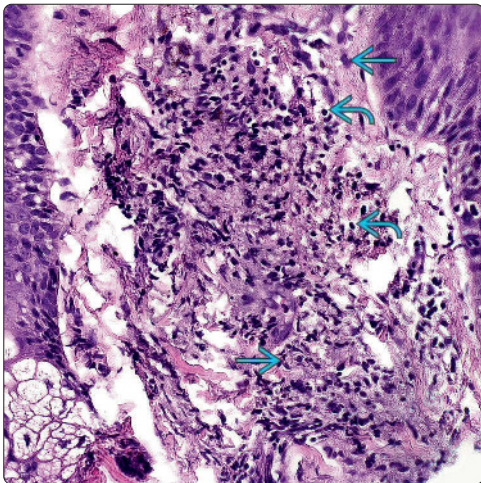


**Perifollicular Lymphocytic Inflammation**

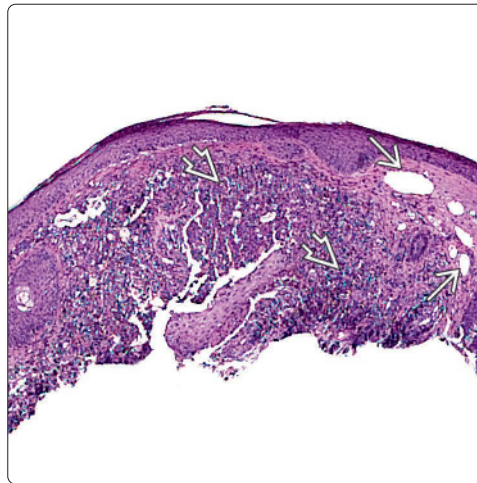


(Left) This high-power view displays follicular plugging with neutrophilic debris [1], which corresponds clinically to pustules, and a perifollicular lymphocytic infiltrate [2]. Telangiectasias are also present [3]. (Right) High-power view shows that the perifollicular infiltrate is lymphocytic [4], suggesting chronic inflammation.

**Chronic Granulomatous Perifollicular Infiltrate**

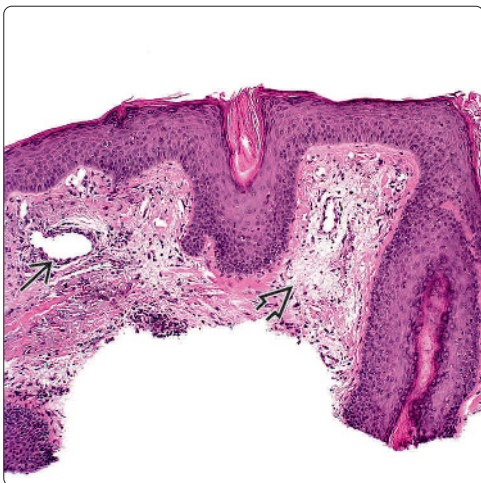


**Telangiectasias in Superficial Dermis**

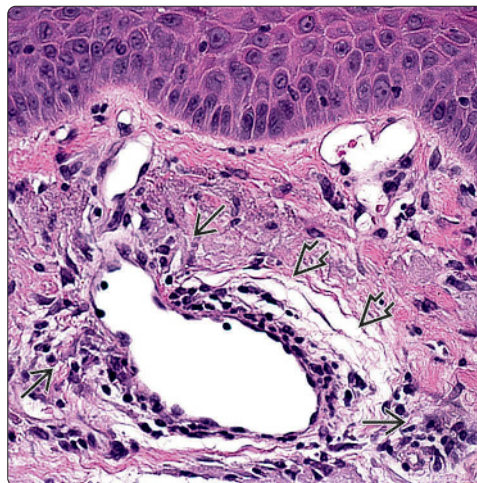


(Left) Higher power view of this skin biopsy confirms that the perifollicular infiltrates in this case are chronic and granulomatous in nature, consisting of histiocytes [1] and lymphocytes [2]. (Right) A low-power photomicrograph of skin of the nose exhibits multiple dilated vessels (telangiectasias) [3] within the superficial dermis. There are also dense basophilic chronic lymphohistiocytic inflammatory infiltrates [4] diffusely infiltrating the superficial to middermis.

**Edema, Telangiectasias, and Mild Chronic Inflammation**



**Telangiectasias, Edema, and Perivascular Inflammation**



(Left) This medium-power image of forehead skin demonstrates dermal edema, seen as patchy white areas in the dermis [1]. Telangiectasias are also present [2]. Mild chronic inflammation is seen in the dermis. (Right) Closer inspection demonstrates perivascular chronic lymphohistiocytic inflammation [3] seen around a telangiectasia. There is also edema [4] present around the telangiectatic vessel.



## KEY FACTS

### TERMINOLOGY

- Chronic disease characterized by follicular occlusion leading to abscesses, draining, sinuses, and scarring of axilla and groin

### CLINICAL ISSUES

- Tender erythematous nodules characterized by
  - Abscesses
  - Draining sinuses
  - Fibrosis and scarring
- Affects intertriginous areas, especially axilla, inguinal, anogenital, and inframammary areas

### MICROSCOPIC

- Early lesions show
  - Follicular plugging, acute folliculitis, and follicular rupture
- Chronic lesions show
  - Chronic folliculitis with deep mixed inflammatory cell infiltrate

- Abscesses, sinus tracts, extensive fibrosis, ± granulation tissue
- Destruction of pilosebaceous units and sweat glands

### TOP DIFFERENTIAL DIAGNOSES

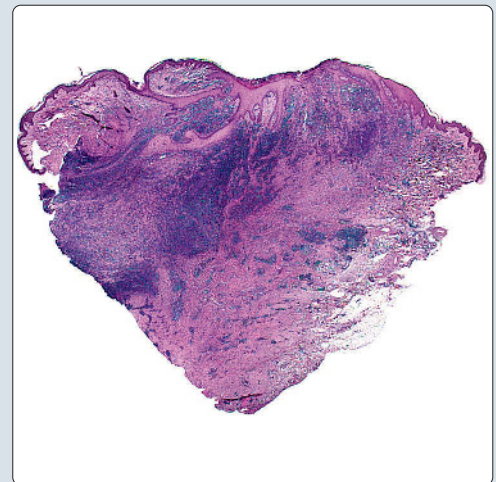
- Chronic deep folliculitis (infectious or noninfectious)
  - Sinus tracts are not usually present
- Abscess
  - Usually solitary
- Follicle rupture
  - Keratin &/or hair in surrounding dermis
- Pyoderma gangrenosum
  - Erythematous nodule that progresses to ulcer
- Crohn disease
  - More granulomatous with neutrophils

Sinus Tracts and Scarring

**(Left)** Erythematous inflammatory nodules, sinus tract formation, and severe scarring of the groin area are shown. (Courtesy E. Newman, MD.) **(Right)** On low power, a dense diffuse inflammatory infiltrate can be seen throughout the dermis. There are reactive changes present in the overlying epidermis.

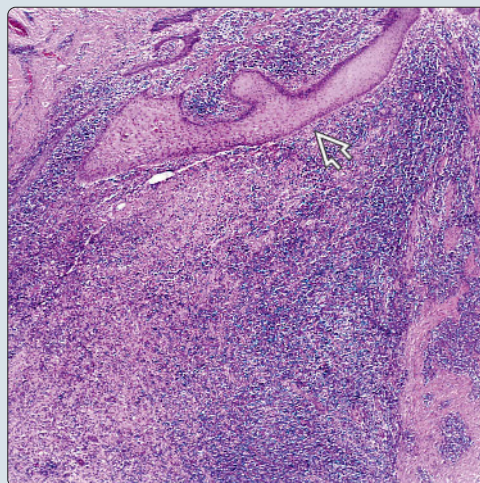


Dense Inflammatory Infiltrate

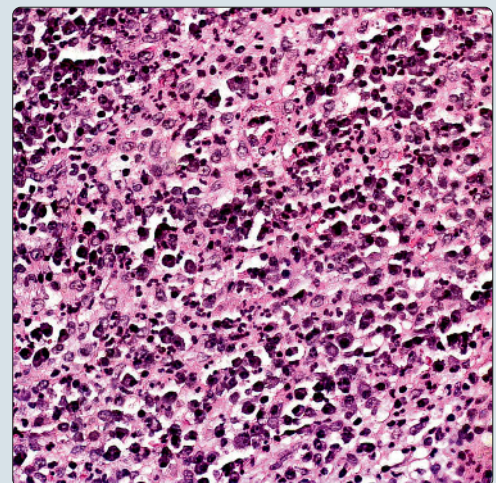


Pseudoepitheliomatous Hyperplasia

**(Left)** There is extension of squamous epithelium into the inflammatory infiltrate. This may represent pseudoepitheliomatous hyperplasia or part of a sinus tract. **(Right)** At high power, the infiltrate is composed of neutrophils, lymphocytes, histiocytes, and plasma cells.



Mixed Inflammatory Infiltrate



## TERMINOLOGY

### Abbreviations

- Hidradenitis suppurativa (HS)

### Synonyms

- Acne inversa, Verneuil disease, pyoderma fistulans significa

### Definitions

- Chronic, relapsing disease characterized by recurrent abscesses, draining sinuses, and scarring of apocrine-bearing areas of skin, especially axilla and groin

## ETIOLOGY/PATHOGENESIS

### Etiology

- Hyperkeratosis of hair follicle leads to occlusion of apocrine glands
  - Subsequent follicular rupture
    - Introduction of keratin and bacteria into surrounding dermis
    - Abscess and sinus tract formation

### Genetic Association

- Locus at chromosome 1p21.1-1q25.3 may be responsible
  - Associated with hidradenitis suppurativa
    - Also seen in diffuse malignant peritoneal mesothelioma

### Disease Associations

- Crohn disease, Dowling-Degos disease, arthropathy, cigarette smoking, and obesity
- HS is part of follicular occlusion tetrad, which includes acne conglobata, dissecting cellulitis, and pilonidal sinuses

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - 1:3,000 to 4:100 depending on study
- Age
  - Onset around puberty
- Sex
  - 3x more common in women than men

### Site

- Intertriginous areas, especially axilla, inguinal, anogenital, and inframammary areas

### Presentation

- Tender erythematous nodules characterized by
  - Abscesses
  - Draining sinuses
  - Fibrosis and scarring

### Treatment

- Surgical approaches
  - Excision with primary closure, graft, or healing with secondary intention
  - Probing sinus tracts and unroofing with secondary intention
- Drugs

- Intralesional or systemic corticosteroids, cyproterone acetate alone, cyproterone acetate plus ethinyl estradiol, isotretinoin, acitretin, TNF- $\alpha$  inhibitors

- Patient driven
  - Weight loss
  - Reduction of friction and moisture

### Prognosis

- Chronic, relapsing

## MICROSCOPIC

### Histologic Features

- Early lesions show
  - Follicular plugging
  - Acute folliculitis
  - Follicular rupture
- Chronic lesions show
  - Chronic folliculitis
    - Mixed inflammatory cell infiltrate in lower 1/2 of dermis and extending into subcutis
  - Abscesses and sinus tracts
    - Often connected to epidermis
  - Extensive fibrosis
  - Destruction of pilosebaceous units and sweat glands
  - $\pm$  granulation tissue

## DIFFERENTIAL DIAGNOSIS

### Chronic Deep Folliculitis (Infectious or Noninfectious)

- Chronic inflammation centered around hair follicle
- Sinus tracts are not usually present

### Abscess

- Usually solitary
- Dense neutrophilic infiltrate  $\pm$  organisms
- Sinus tracts are not present

### Follicle Rupture

- Acute &/or chronic inflammation centered on hair follicle
- Keratin &/or hair in surrounding dermis
- Sinus tracts are not usually present

### Pyoderma Gangrenosum

- Erythematous nodule that progresses to ulcer
- Single or multiple lesions
- Abscess with mixed inflammation
- Necrosis
- Vasculitis often present

### Crohn Disease

- Suppurative folliculitis
- Abscesses
- More granulomatous with neutrophils
- Sinus tracts are not present

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# Furuncle

## KEY FACTS

### TERMINOLOGY

- Single, painful, firm to fluctuant mass of walled-off purulent material originating from hair follicle

### ETIOLOGY/PATHOGENESIS

- Usually caused by *Staphylococcus aureus*, particularly Methicillin-resistant *S. aureus*

### CLINICAL ISSUES

- Common sites
  - Neck, face, buttocks, axillae, and groin
- Infection begins around hair follicle and extends into deep dermis and can spread laterally
- Develops into fluctuant mass

### MACROSCOPIC

- Acutely developing (days), painful lesion

### MICROSCOPIC

- Follicular and perifollicular dermal inflammation composed predominately of neutrophils
- Follicular obliteration with pustule formation &/or foreign body-type reaction
- Degenerate hair follicle, hair shaft, and keratinaceous debris may be present

### TOP DIFFERENTIAL DIAGNOSES

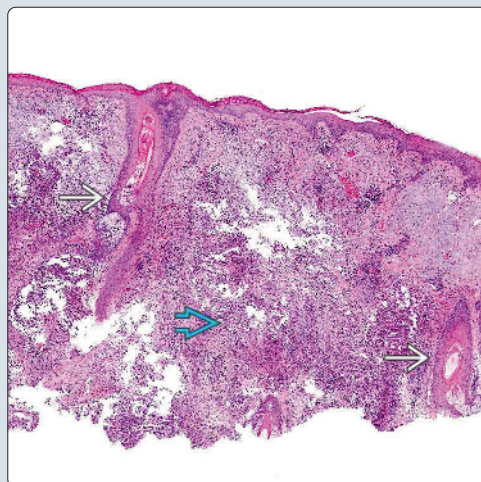
- Folliculitis
- Carbuncle
- Hidradenitis suppurativa
- Acne keloidalis nuchae
- Acne conglobate

### Solitary Erythematous Nodule

(Left) A painful, solitary, erythematous nodule in the axilla of a 23-year-old woman is shown. This lesion had been slowly growing for 5 days. (Right) Low magnification of an excisional biopsy demonstrates a dense, mixed inflammatory infiltrate involving a wide swath of tissue in the mid to deep dermis. Follicles and sebaceous glands are associated with the inflammation.

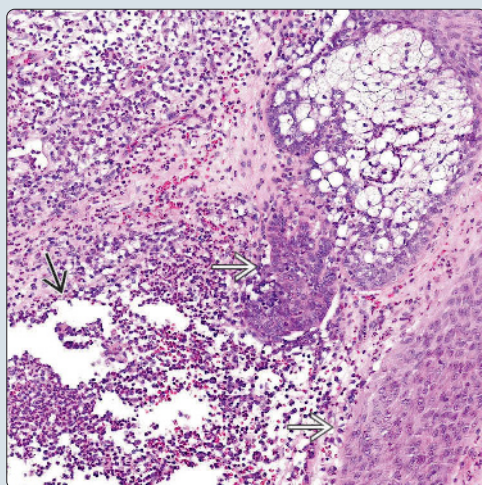


### Dense Mid to Deep Perifollicular Infiltrate

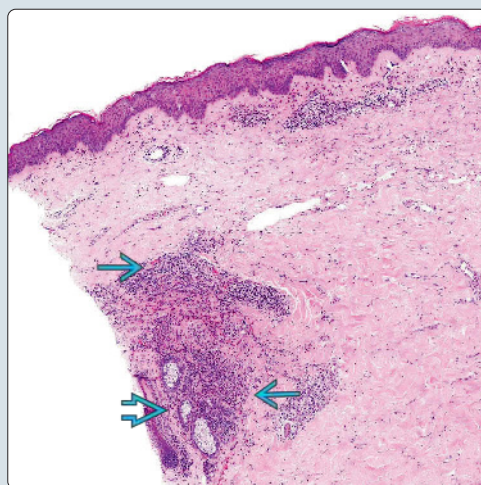


### Follicular Destruction by Neutrophilic Inflammation

(Left) The follicular epithelium is being destroyed by the predominately neutrophilic inflammation. Adjacent pustule formation is also present. (Right) Punch biopsy demonstrates an acute inflammatory infiltrate. The adjacent folliculosebaceous unit is involved; however, the process appears to be limited to a relatively focal area.



### Dense Perifollicular Inflammation





**TERMINOLOGY****Synonyms**

- Furunculosis, deep folliculitis, abscess, boil, uncomplicated skin and skin structure infections, skin and soft tissue infections

**Definitions**

- Single, painful, firm to fluctuant mass of walled-off purulent material originating from hair follicle

**ETIOLOGY/PATHOGENESIS****Infectious Agents**

- Usually caused by *Staphylococcus aureus*, particularly Methicillin-resistant *S. aureus*
  - Associated with staphylococcal Panton-Valentine leukocidin (PVL) virulence factor
  - Recurrent furunculosis is strongly associated with PVL virulence factor and nasal carriage of Methicillin-resistant *S. aureus*
- May occur following antimicrobial drug treatment that allows pathogenic bacteria to multiply on skin
- May occur as complication of Myiasis

**Inciting Factors**

- Friction, pressure, scratching
- Hyperhidrosis
- Foreign body/foreign body reaction

**Risk Factors**

- Poor hygiene, diabetes, obesity, lymphoproliferative disorders, immunosuppressant drugs, HIV/AIDS

**CLINICAL ISSUES****Epidemiology**

- More common in adolescents
- More common in hospitalized &/or immunosuppressed patients
- More common in patients with impaired skin integrity (burns or wounds)
- Risk factors
  - Poor hygiene, older age, cardiopulmonary or hepatorenal disease, diabetes mellitus, debility, peripheral arteriovenous or lymphatic insufficiency, and trauma

**Presentation**

- Common sites
  - Neck, face, buttocks, axillae, and groin
- Infection begins around hair follicle and extends into deep dermis and can spread laterally
- Develops into fluctuant mass
- May spontaneously drain to skin surface

**Prognosis**

- Excellent with proper treatment

**MACROSCOPIC****General Features**

- Acutely developing (days), painful lesion
- Pustule with surrounding rim of erythema

- Firm, erythematous nodule

**MICROSCOPIC****Histologic Features**

- Follicular and perifollicular dermal inflammation composed predominately of neutrophils
- Follicular obliteration with pustule formation &/or foreign body-type reaction
- Degenerate hair follicle, hair shaft, and keratinaceous debris may be present
- Extension of the process into subcutis may occur

**ANCILLARY TESTS****Bacterial Culture**

- Debrided material should be sent for culture and antibiotic susceptibility testing
- Particularly if recurrent or resistant to therapy

**Ultrasound**

- May be useful in distinguishing from other lesions

**DIFFERENTIAL DIAGNOSIS****Folliculitis**

- Papular or pustular inflammation of hair follicles

**Carbuncle**

- Network of furuncles connected by sinus tracts

**Hidradenitis Suppurativa**

- Recurrent painful suppurative or inflammatory lesions in the axillae or groin
- Exclusive to axillae or groin

**Acne Keloidalis Nuchae**

- Chronic, follicular-based inflammation, targeting multiple follicles on occipital scalp, posterior neck, and upper back

**Acne Conglobate**

- Acneiform eruption with chronic inflammation, resulting in keloidal and atrophic scarring on chest, back, extremities, and face

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# Eosinophilic Pustular Folliculitis

## KEY FACTS

### TERMINOLOGY

- Synonym: Eosinophilic folliculitis
- Inflammation of follicles with numerous eosinophils
- 3 classic forms
  - Infancy
  - Immunosuppressed patients (most often secondary to HIV)
  - Adults (especially 3rd/4th decade of life)

### CLINICAL ISSUES

- Erythematous papules and pustules
- Pruritus often severe in immunosuppressed patients
- In infancy
  - Discrete papules and pustules
  - May be clustered on scalp

### MICROSCOPIC

- Inflammation of hair follicles with predominance of eosinophils

### TOP DIFFERENTIAL DIAGNOSES

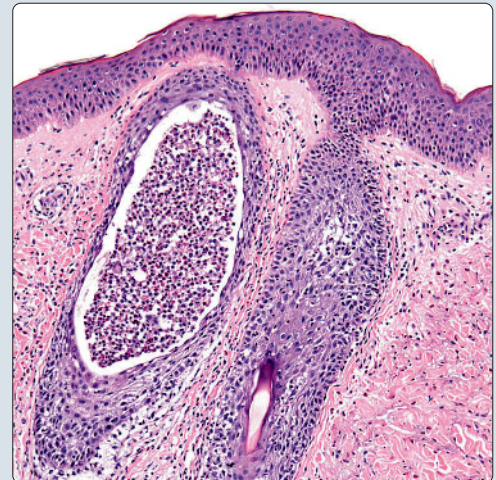
- Majocchi granuloma
  - May have identical features to eosinophilic folliculitis
  - Fungal hyphae are present
- Acneiform lesions
  - Tend to have mixed inflammation (neutrophils, lymphocytes, eosinophils) in and around follicle
- Folliculitis (bacterial)
  - Tend to have mixed inflammation (lymphocytes, neutrophils, eosinophils) in dermis/perifollicular areas
  - Gram staining may be positive
  - Bacterial culture of pustules may be necessary
- Folliculitis (herpetic)
  - Follicular/sebaceous necrosis, acantholytic cells, viral cytopathic change, multinucleate cells may be evident

**Erythematous Folliculocentric Papules**

*(Left) In this example of eosinophilic folliculitis, there are erythematous, folliculocentric papules on the trunk of this infant. (Courtesy R. Antaya, MD.) (Right) In eosinophilic folliculitis, there is a predominance of eosinophils within and around hair follicles.*

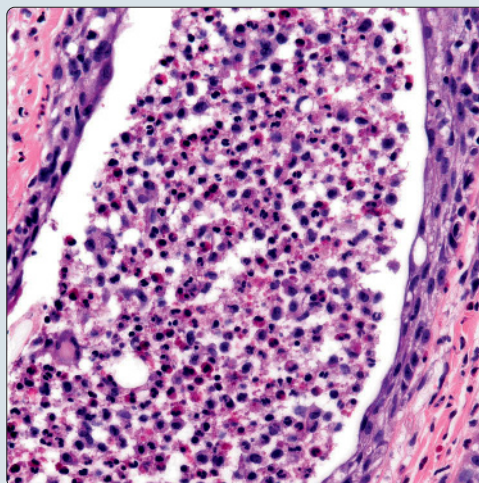


**Eosinophils Within Hair Follicle**

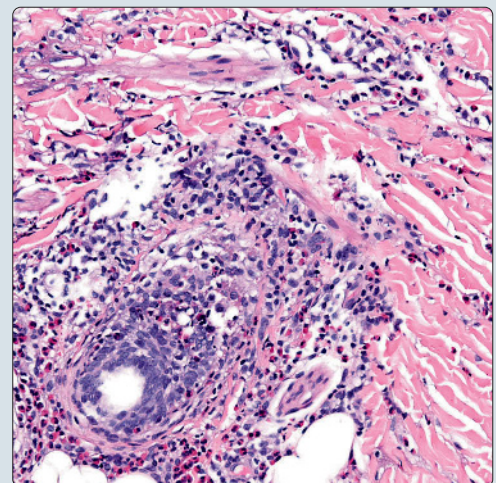


**Follicle Filled With Numerous Eosinophils**

*(Left) In eosinophilic folliculitis, follicles are inflamed with numerous eosinophils. (Right) In this example of eosinophilic folliculitis from an infant, a hair follicle is surrounded by a predominance of eosinophils.*



**Numerous Perifollicular Eosinophils**



## TERMINOLOGY

### Synonyms

- Eosinophilic folliculitis
- Ofuji disease

### Definitions

- Inflammation of follicles with numerous eosinophils
- 3 classic forms
  - Infancy
  - Immunosuppressed patients (most often secondary to HIV)
  - Adults (especially 3rd/4th decade of life)

## ETIOLOGY/PATHOGENESIS

### Unknown

- May represent hypersensitivity reaction to unknown antigens in
  - Bacteria
  - *Demodex*
  - Medications
  - Sebocytes
  - Other

## CLINICAL ISSUES

### Epidemiology

- Age
  - Presents in
    - Infancy
    - Adulthood
- Sex
  - Male predominance for all 3 forms

### Site

- In infants, 1st few weeks of life
  - Often on scalp
  - May spread to other parts of body
- In adults
  - Immunocompromised
    - Often on trunk (but may affect face)
    - Eosinophilic folliculitis is 1 AIDS-defining illness
  - Nonimmunocompromised, "classic" form
    - On face, trunk, upper extremities ("seborrheic" areas)
    - Rarely on palms/soles
    - Most commonly described in Japanese patients

### Presentation

- Erythematous papules and pustules in "classic" form
  - May form circinate/annular arrangements
  - May be superimposed on plaques
  - Lesions often recurrent
- Pruritus often severe in immunosuppressed patients
  - Papules often excoriated
  - Papules often discrete (rather than clustered/superimposed on plaques as in "classic" form)
- In infancy
  - Discrete papules and pustules
  - May be clustered on scalp
- Rarely in butterfly facial distribution with few/no papules/pustules

## Laboratory Tests

- Peripheral eosinophilia may be present
- Check immune status (i.e., HIV status) as indicated
- Culture of pustules is negative

## Treatment

- For all forms
  - Topical corticosteroids
  - UVB light treatment

## Prognosis

- Chronic, relapsing course for "classic" form
- Good prognosis for form in infancy
- Improvement of immunosuppression necessary in immunosuppressed patients

## MICROSCOPIC

### Histologic Features

- Inflammation of hair follicles
- Numerous eosinophils
- Follicular infundibulum &/or adjacent epidermis may show spongiosis or mucinosis
- Dermal flame figures may be evident
- Rarely, follicles may be destroyed

## ANCILLARY TESTS

### Histochemistry

- PAS diastase
  - Staining pattern: Negative for fungus

## DIFFERENTIAL DIAGNOSIS

### Majocchi Granuloma

- Clinical
  - Erythematous papules
  - May see secondary changes
- Histopathologic
  - May have identical features to eosinophilic folliculitis
  - Fungal hyphae (PAS positive) present

### Acneiform Lesions

- Tend to have mixed inflammation (lymphocytes, neutrophils, eosinophils) in dermis/perifollicular areas

### Folliculitis (Bacterial)

- Tend to have mixed inflammation (neutrophils, lymphocytes, eosinophils) in and around follicle
- Gram staining may be positive
- Bacterial culture of pustules may be necessary

### Folliculitis (Herpetic)

- Tend to have mixed inflammation (neutrophils, lymphocytes, eosinophils) in and around follicle
- Follicular/sebaceous necrosis, acantholytic cells, viral cytopathic change, multinucleate cells may be evident

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## KEY FACTS

### CLINICAL ISSUES

- Age
  - 13-35 years
- Sex
  - M:F = 1:10
- Incidence
  - Rare
- Ethnicity
  - No racial predilection
- Prognosis
  - Prolonged course but remits after menopause
- Presentation
  - Apocrine distribution
  - Primarily axilla, periareolar, and anogenital areas
  - Monomorphic discrete flesh-colored papules
  - Intense pruritus

### MICROSCOPIC

- Keratotic plugging of infundibulum
- Follicular epidermal spongiosis and vesiculation
- Perifollicular and periductal inflammation
- Lymphocytes and occasionally eosinophils
- Inflammation does not usually involve sweat glands
- ± rupture of associated apocrine gland
- Perifollicular foam cells are common

### TOP DIFFERENTIAL DIAGNOSES

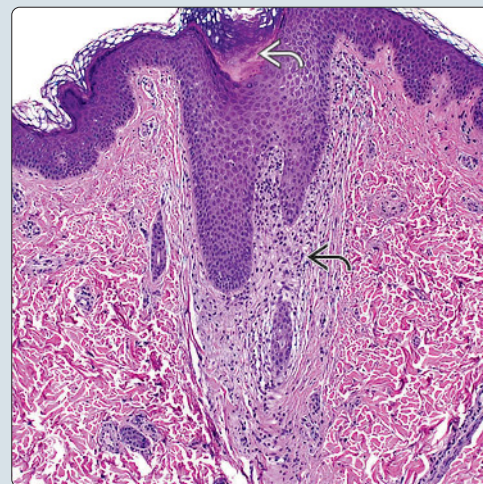
- Pityriasis rubra pilaris
- Folliculitis
- Acne
- Miliaria
- Keratosis pilaris
- Lichen spinulosus
- Hidradenitis suppurativa

Small Flesh-Colored Papules

(Left) Fox-Fordyce disease is characterized by grouped papules in the groin and the axilla. (Courtesy N. Agim, MD.) (Right) There is a follicular plug obstructing the follicle and eccrine duct ostium. There is a surrounding mild, perifollicular and periadnexal, lymphocytic infiltrate.

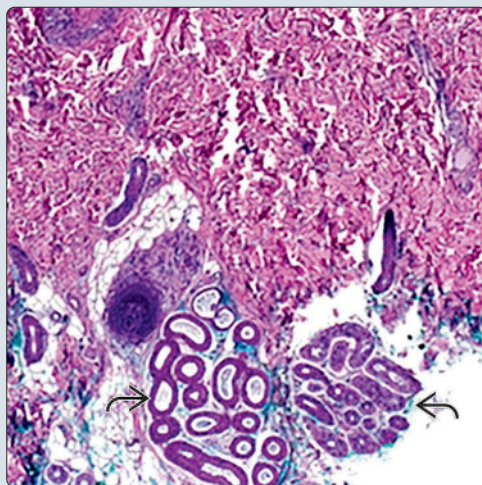


Follicular Plugging With Mild Spongiosis

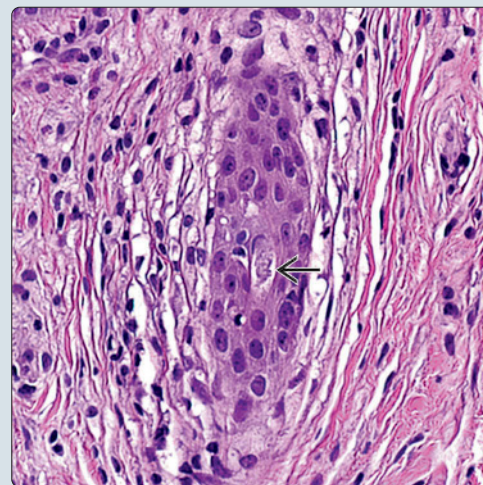


Absent Deep Inflammation

(Left) In the deep dermis and subcutis, the eccrine glands are uninvolved by inflammation. (Right) This eccrine duct has secretions filling the lumen, which is plugged at the follicular infundibulum. There is a very mild surrounding lymphocytic infiltrate with faint mucin deposition.



Sweat Duct Plugging



## TERMINOLOGY

### Synonyms

- Apocrine miliaria

### Definitions

- Keratin plugging of apocrine glands resulting in sweat retention and rupture of superficial apocrine duct

## ETIOLOGY/PATHOGENESIS

### Unknown

- Multiple possible triggers
  - Hormonal factors, emotional/physical

### Keratin Plugging of Apocrine Glands

- Causes sweat retention
- Ultimately distention and rupture of gland

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Rare
- Age
  - 13-35 years
- Sex
  - 90% female
- Ethnicity
  - No racial predilection

### Site

- Apocrine distribution
  - Primarily axilla, periareolar, and anogenital areas
  - Less commonly, medial thighs, periumbilical, and sternal regions

### Presentation

- Monomorphic discrete flesh-colored papules
- Intense pruritus
- Hair density typically reduced

### Treatment

- Responds to estrogen
  - Pregnancy and oral contraception may alleviate itching
- Topical and intralesional steroid injections, tretinoin, and clindamycin lotion have all been somewhat effective in relieving inflammation
- Surgical excision
- Botulinum toxin-A (Botox) injection
- Intense pulsed light or fractional CO<sub>2</sub> laser

### Prognosis

- Prolonged course but remits after menopause

### Associated Illnesses

- Has been reported in cases of Turner syndrome

## MICROSCOPIC

### Histologic Features

- Keratotic plugging of infundibulum
- Follicular epidermal spongiosis and keratinocyte vesiculation

- Perifollicular and periductal inflammation
  - Lymphocytes and occasionally eosinophils
  - Inflammation does not usually involve sweat glands
- ± rupture of associated apocrine gland
- Perifollicular foam cells are common
  - Also mucin, fibrosis, &/or mast cells

## DIFFERENTIAL DIAGNOSIS

### Histopathological

- Pityriasis rubra pilaris
  - Superficial perivascular and perifollicular lymphocytic infiltrate
  - Alternating orthokeratosis and parakeratosis
    - Checkerboard pattern
  - Psoriasiform hyperplasia with hypergranulosis
  - Follicular plugging
- Folliculitis
  - Acute &/or chronic inflammation centered around follicle
  - Clinically may or may not be itchy
  - Clinically not limited to axilla or other apocrine sites (more widespread)
  - May see hair coming out middle of it clinically
- Acne
  - Keratin plug of hair follicle
    - Bacterial proliferation in follicular lumen
  - Inflammation around hair follicle
    - May be acute, chronic, &/or granulomatous
  - Clinically typically located on face, upper back, upper chest
  - Often multiple morphologies clinically
    - Open comedones, closed comedones, papules, cysts, pustules
    - Fox-Fordyce shows papules (one morphology)

### Clinical

- Folliculitis
  - Acute &/or chronic inflammation centered around hair follicle
  - May have organisms in follicle
- Acne
  - Keratin plug of hair follicle
    - Bacterial proliferation in follicular lumen
  - Inflammation around hair follicle
    - May be acute, chronic, &/or granulomatous
- Keratosis pilaris
  - Mostly on arms and thighs of younger patients
  - Follicular plugging
  - Perifollicular inflammation
    - Lymphocytes &/or neutrophils
  - ± perifollicular fibrosis

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# Chloracne

## KEY FACTS

### TERMINOLOGY

- Acneiform eruption caused by exposure to halogenated chemicals

### ETIOLOGY/PATHOGENESIS

- Precipitated by environmental exposure to halogenated chemicals including dioxins
- Major exposure event in Vietnam war with Agent Orange

### CLINICAL ISSUES

- Open comedones without inflammatory lesions
- Predominantly on cheeks and postauricular areas
- Associated hyperpigmentation and hypertrichosis
- Identification and removal of source of exposure is necessary

### MICROSCOPIC

- Open comedones
- Orthohyperkeratosis

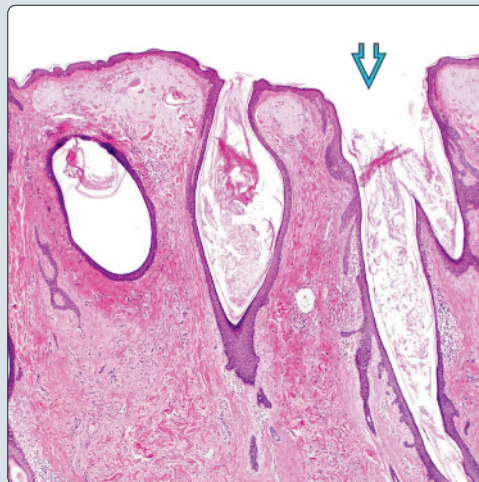
- Milia
- Infundibular cysts
- Diminished or lost sebaceous lobules
- Solar elastosis in dermis

### TOP DIFFERENTIAL DIAGNOSES

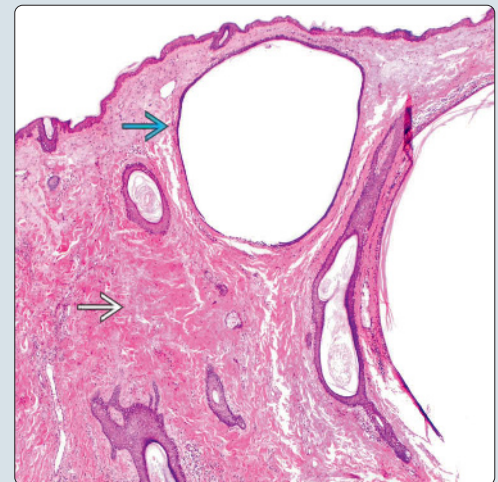
- Acne vulgaris
  - Clinically presents with inflammatory papules, as well as closed comedones
- Favre-Racouchot
  - Histologically has prominent nodular solar elastosis
- Acne rosacea
  - Lacks comedones
  - Perifollicular inflammation with retained sebaceous lobules
- Sorafenib-associated facial acneiform eruption
  - Limited to patients being treated with sorafenib

#### Comedone Openings in Chloracne

(Left) Image shows dilated comedonal openings [red box] in chloracne. Widened follicular ostia are filled by keratin debris and invaginate deeply. (Right) Dermal collagen becomes fibrotic [red box], and milia [red box] are seen. Collagen bundles become thicker and compressed, with entrapment of milia cysts.

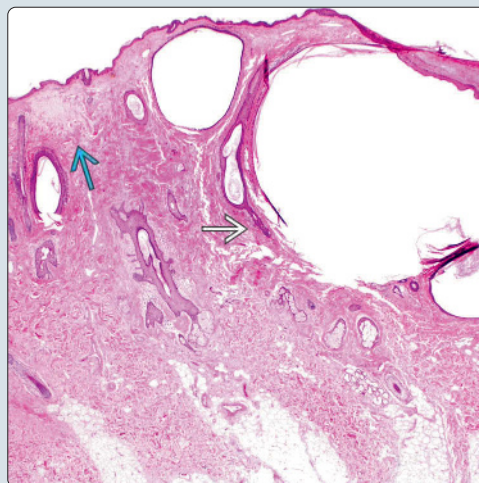


#### Dermal Fibrosis and Milia in Chloracne

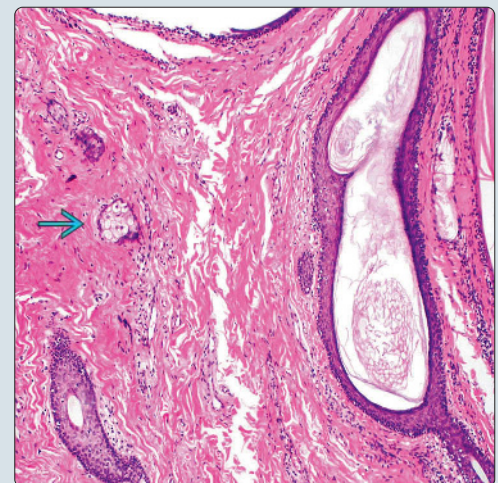


#### Solar Elastosis With Milia

(Left) Solar elastotic material [red box] and milia [red box] are seen in the dermis. Blue-gray coiled elastic fibers in the dermis indicate chronic sun damage. (Right) Sebaceous lobules become atrophic [red box] in chloracne, diminished in size and number.



#### Atrophic Sebaceous Lobules in Chloracne





**TERMINOLOGY****Synonyms**

- Occupational acne

**Definitions**

- Acneiform eruption caused by exposure to halogenated chemicals

**ETIOLOGY/PATHOGENESIS****Environmental Exposure**

- Chronic or acute exposure to halogenated chemicals including
  - Dioxin (dibenzofurans)
  - Naphthalene
  - Chlorinated biphenyl
  - Agent Orange defoliant
- Historical large-scale exposure events
  - 1949 chemical plant explosion in West Virginia
  - 1976 chemical plant explosion in Seveso, Italy
  - Vietnam War: Agent Orange (2, 3, 7, 8-tetrachlorodibenzo-p-dioxin)

**CLINICAL ISSUES****Epidemiology**

- Incidence
  - Rare
    - Limited to occupational or environmental exposures
- Sex
  - More common in men
    - Probably related to historical occupational and war exposures, which involved predominantly men

**Presentation**

- Noninflammatory open comedones on malar crescent and postauricular areas
- Milia and cysts filled with straw-colored fluid
- May progress to involve neck, buttocks, genitals
- Associated hyperpigmentation and hypertrichosis

**Treatment**

- Identification and removal of source of exposure is paramount
  - Most lesions clear within 2 years after exposure is stopped
    - Some cases may persist longer

**Prognosis**

- Chloracne fades slowly after cessation of exposure

**MICROSCOPIC****Histologic Features**

- Dilated follicular ostia filled by orthohyperkeratosis (comedones)
- Dermal fibrosis and milia formation
- Melanin granules in stratum corneum
- Diminished sebaceous lobules
  - Sebaceous glands may disappear completely
- Solar elastosis in dermis

**ANCILLARY TESTS****Serologic Testing**

- Dioxin levels may be measured in serum

**DIFFERENTIAL DIAGNOSIS****Acne Vulgaris**

- Clinically presents with inflammatory papules, as well as closed comedones
- Open comedones and noninflammatory lesions predominate in chloracne

**Favre-Racouchot**

- Presents in chronically sun-exposed areas
  - Lacks hyperpigmentation
  - No hypertrichosis
- Histologically has prominent nodular solar elastosis
- May have closed comedones

**Acne Rosacea**

- Lacks comedones
- Inflammatory papules predominate
- Perifollicular inflammation with retained sebaceous lobules

**Sorafenib-Associated Facial Acneiform Eruption**

- Exceedingly rare (5 cases reported)
- Can present as open and closed comedones with similar appearance and distribution to chloracne
- Can also present as papules and pustules
- Limited to patients being treated with sorafenib
- Lowering dose or discontinuing sorafenib results in resolution or improvement

**DIAGNOSTIC CHECKLIST****Clinically Relevant Pathologic Features**

- Noninflammatory, open comedones impart resemblance to comedonal acne vulgaris

**Pathologic Interpretation Pearls**

- Open comedones predominate
- Sebaceous lobules diminished

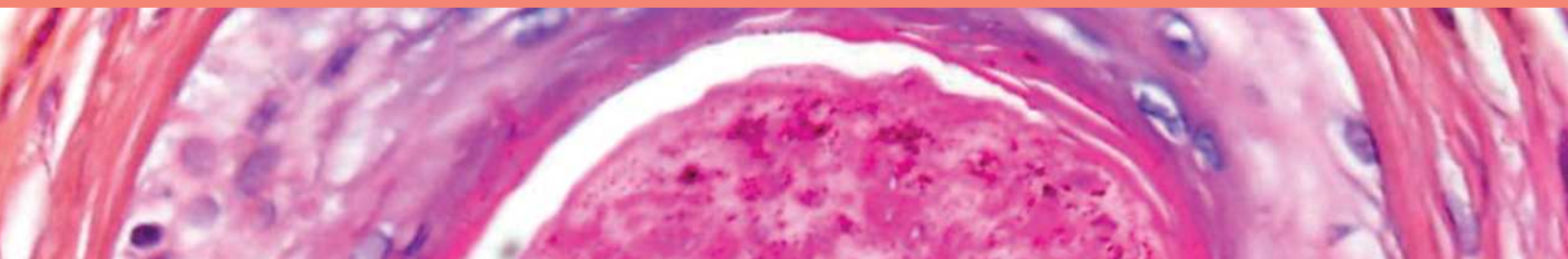
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## SECTION 12

# Alopecias



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# Androgenetic Alopecia

## KEY FACTS

### ETIOLOGY/PATHOGENESIS

- Polygenic inheritance

### CLINICAL ISSUES

- Symmetric thinning across vertex (female pattern)
- Frontal recession (male pattern)
- Bitemporal recession (male pattern)

### MACROSCOPIC

- Hairs of variable thickness
- Brown dots from perifollicular inflammation

### MICROSCOPIC

- Few follicles present in vertical sections
- Solar elastosis
- Seborrheic folliculitis and enlarged sebaceous glands relative to hair follicles
- Vellus-like follicles in superficial dermis
- > 20% vellus-like follicles

- > 20% telogen hairs
- Anisotrichosis: Variation in hair fiber caliber

### TOP DIFFERENTIAL DIAGNOSES

- Chronic telogen effluvium
- Diffuse alopecia areata
- Cicatricial alopecia
- Trichotillomania

### DIAGNOSTIC CHECKLIST

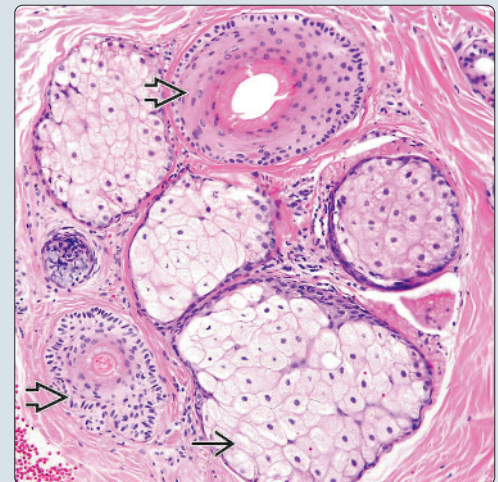
- Scalp biopsy that looks like facial skin: Think androgenetic alopecia (AGA)
- AGA may be commingled with other alopecias
- Eventually, follicular stela become subfollicular scars
- Since AGA is common, it may be commingled with other alopecias

#### Symmetric Thinning of Hair at Vertex

(Left) Symmetric thinning of the hair across the vertex in this case of female pattern androgenetic alopecia (AGA) is associated with basal cell carcinoma [2]. (Courtesy T. Kestenbaum, MD.) (Right) There is striking variation in the size of the follicles [2], some of which are dwarfed by the sebaceous gland [2].

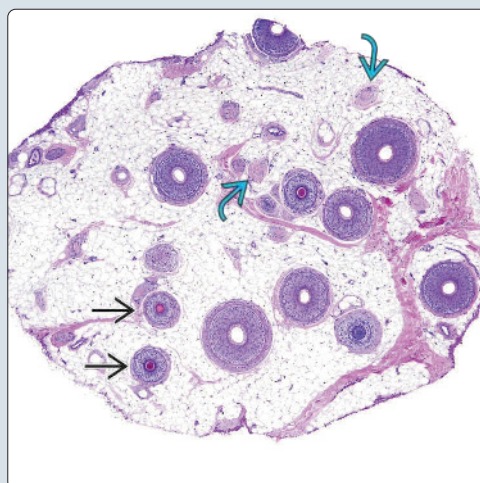


#### Striking Variation of Follicle Size

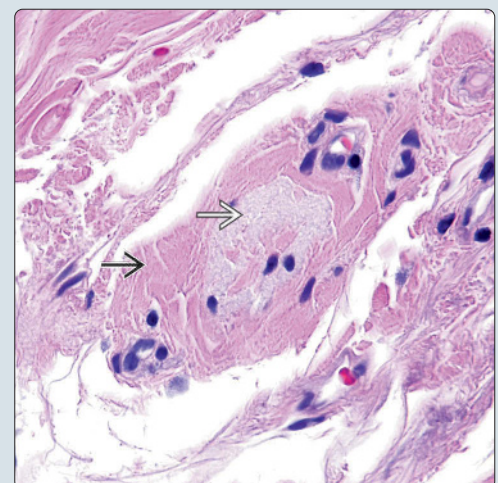


#### Low-Power Variation in Size With Miniaturization and Numerous Stelae

(Left) This horizontal section taken at the level of the subcutis/deep dermis demonstrates striking variation in follicle size with miniaturization [2] as well as numerous stelae [2], indicative of advanced AGA. (Right) The deepest segment of the stela has been without an actively growing hair for the longest period of the time and eventually becomes a solid column comprised of mature collagen [2] and amorphous blue elastoid material [2].



#### Stela



## TERMINOLOGY

### Abbreviations

- Androgenetic alopecia (AGA)

### Synonyms

- Common balding, male and female pattern alopecia

### Definitions

- Androgen-mediated nonscarring alopecia

## ETIOLOGY/PATHOGENESIS

### Genetic

- Polygenic inheritance
- Increased type II 5 $\alpha$ -reductase and androgen receptors in balding hair papillae
- Potentiates effects of dihydrotestosterone on scalp follicles, resulting in shortened anagen cycles and gradual hair miniaturization

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - 6% of women by age 50, increasing to 38% by age 70
  - 58% of men by age 50, increasing to 80% by age 70

### Presentation

- Female pattern
  - Symmetric Christmas tree pattern thinning across midline of vertex
  - Sparing frontal hairline
- Male pattern
  - Frontal recession
  - Bitemporal recession
  - Mid scalp and vertex hair loss

### Laboratory Tests

- In women, TSH and ferritin
  - Hypothyroidism and iron deficiency may produce telogen effluvium that mimics AGA

## MACROSCOPIC

### Processing Skin Biopsies in Alopecia

- Nonscarring alopecias: Process horizontally
- Scarring alopecias: Process vertically
- If clinician is uncertain
  - Recommend 2 biopsies
    - Process 1 biopsy horizontally
    - Bisect 2nd biopsy and process 1/2 vertically and send 1/2 for direct immunofluorescence

### Dermoscopic Findings

- > 20% thin hairs from follicular miniaturization
- Hairs of variable thickness
- Brown dots from perifollicular inflammation

## MICROSCOPIC

### Histologic Features in Vertical Sections

- Few follicles present in vertical sections

- Solar elastosis in advanced cases involving sun-exposed fair skin
- Sebaceous gland hyperplasia
- Lymphohistiocytic inflammation around lower infundibulum/upper isthmus (seborrheic folliculitis)
- Angiofibrotic streaks (stelae) beneath vellus-like follicles
- Arao-Perkins bodies
  - Globes of elastin arranged in vertical array like ladder rungs adjacent to stelae, representing site of previous follicular papillae
  - Best demonstrated with orcein-Giemsa histochemical preparation

### Histologic Features in Horizontal Sections

- > 20% small diameter, vellus-like hairs
  - Vellus-like follicles are located in superficial dermis and have hair fibers < 0.03 mm in diameter or decreased thickness of inner root sheath
- > 20% telogen hairs
- Perifollicular fibrosis around lower infundibulum/upper isthmus
- Anisotrichosis: Variation in hair fiber caliber
- Over time, stelae become collagenized and become subfollicular scars that are no longer responsive to medical therapy

## DIFFERENTIAL DIAGNOSIS

### Chronic Telogen Effluvium

- Increased telogen hairs, but no follicular miniaturization

### Diffuse Alopecia Areata

- Peribulbar lymphocytic dermatitis with eosinophils and dystrophic nanogen follicles
- Melanin pigment and eosinophils in stelae
- Follicles uniformly miniaturized with less diversity in hair size than AGA
- No sebaceous gland enlargement or seborrheic folliculitis

### Cicatricial Alopecia

- Follicular scars instead of vascularized stelae (elastic fibers absent in follicular scars)

### Trichotillomania

- Melanin pigment casts and trichomalacia with increased catagen hairs
- No follicular miniaturization

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Scalp biopsy that looks like facial skin: Think AGA
- Disproportionately large sebaceous glands and arrector pili muscles are clues to follicular miniaturization
- Over time, stelae become scars and may be misinterpreted as primary cicatricial alopecia
- Since AGA is common, it may be commingled with other alopecias

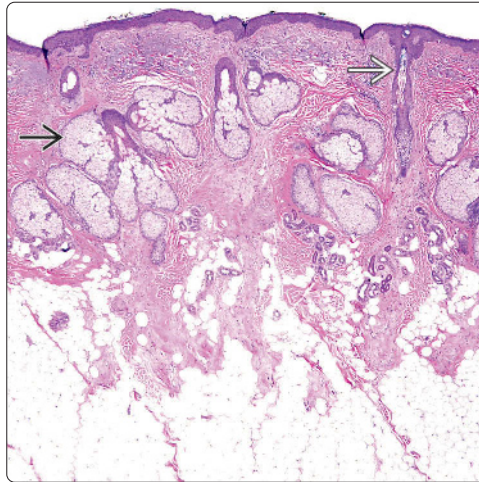
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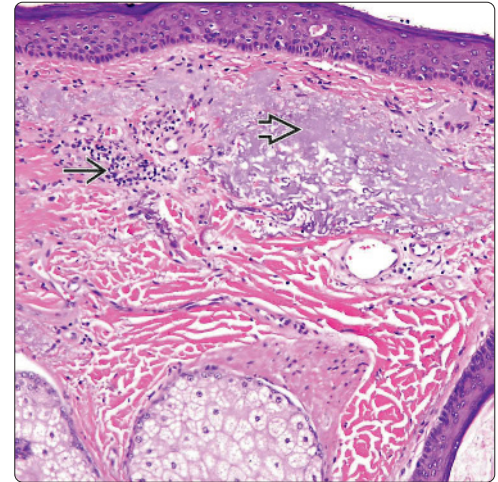


## Small and Superficial Hair Follicles With Prominent Sebaceous Glands

(Left) Normal scalp contains many large subcutaneous hair follicles. A biopsy from a scalp with AGA looks like facial skin because the hair follicles are small and superficial with prominent sebaceous glands. (Right) Individuals with AGA often exhibit signs of sun damage such as solar elastosis and lentigo-like epidermal pigmentation. These changes mimic sun-damaged facial skin. There is often sparse inflammation in AGA.

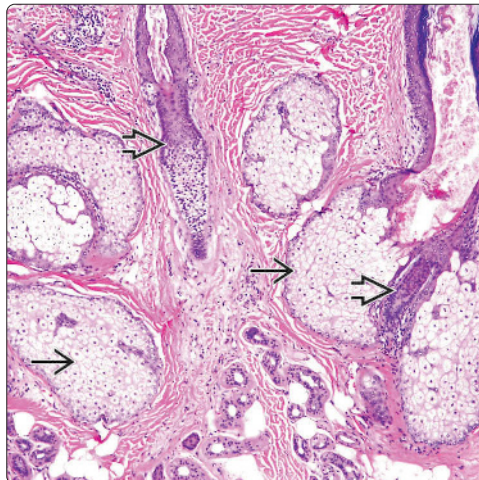


## Solar Elastosis

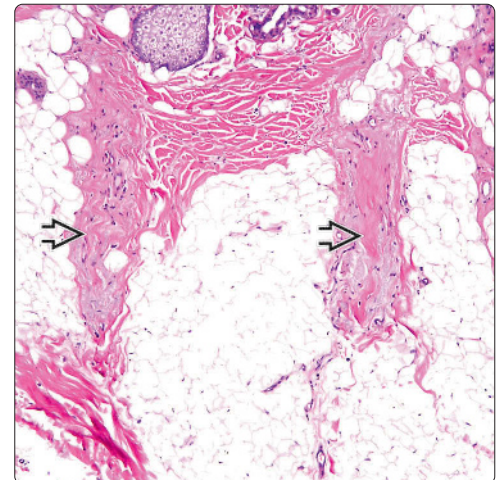


## Vellus-Like Follicles

(Left) Vellus-like follicles are dwarfed by companion sebaceous glands. Whether the apparent enlargement of sebaceous glands in AGA is an optical illusion or genuine is still debated. (Right) Angiofibrotic streamers beneath vellus-like follicles are known as "stelae," the stone markers used as tombstones by the ancient Egyptians, Greeks, and Romans to honor the dead. Stelae become fibrotic with progressive AGA; eventually, they become subfollicular scars.

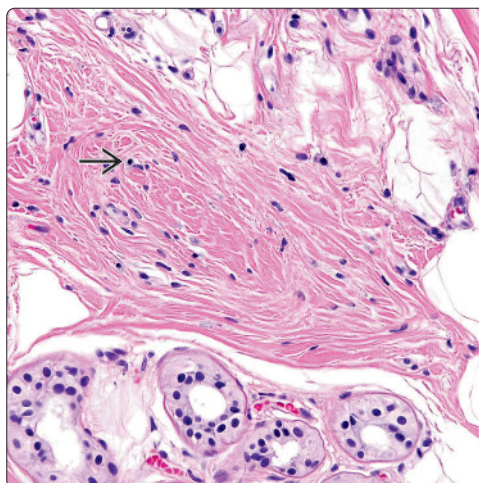


## Fibrotic Stelae

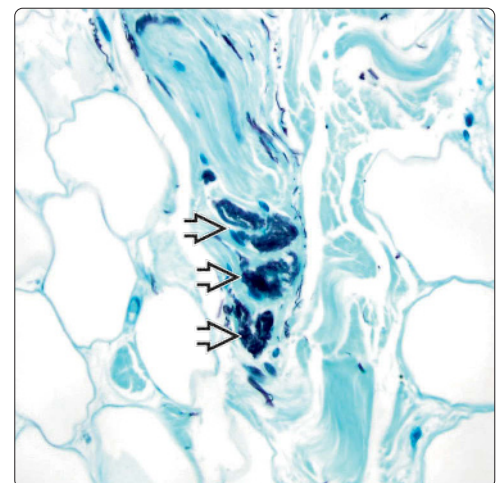


## Stela With Mast Cells

(Left) Stelae often contain mast cells. (Right) Orcein-Giemsa stain reveals a string of Arao-Perkins bodies. These structures are purported to represent the resting sites of previous follicular papillae. The hair follicles in AGA become progressively smaller and more superficial with each hair growth cycle. The papilla develops slightly higher in the dermis with each cycle, producing a ladder rung arrangement of Arao-Perkins bodies.

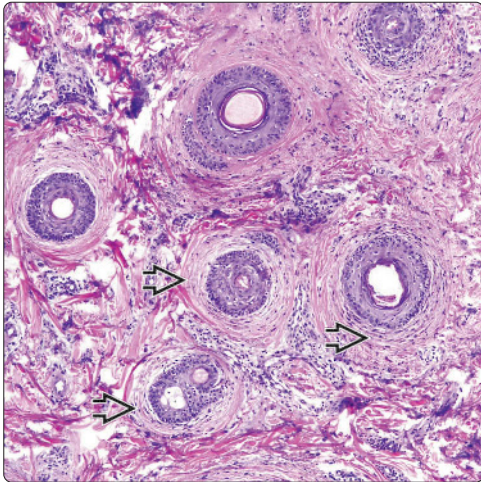


## Arao-Perkins Bodies

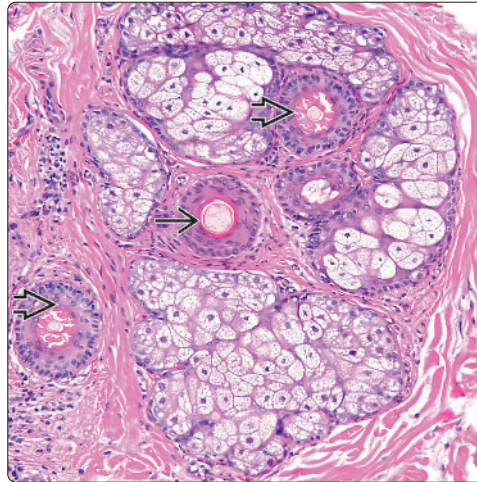




**Concentric Perifollicular Fibrosis**

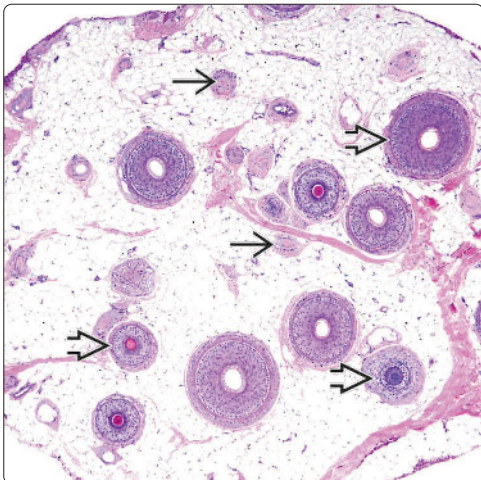


**Disproportionately Large Sebaceous Glands**

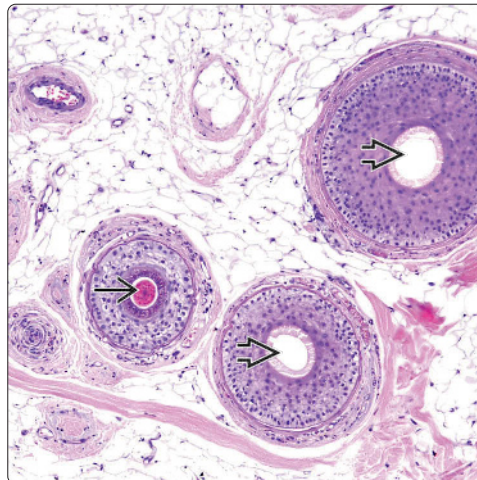


(Left) Horizontal section through the upper portion of the hair follicles reveals concentric perifollicular fibrosis [ ] and sparse perifolliculitis without signs of follicular injury. (Right) Horizontal section at the level of the isthmus reveals disproportionately large sebaceous glands associated with miniaturized vellus-like hairs [ ]. Note the telogen hair without an inner root sheath [ ]. The percentage of telogen hairs is increased in AGA.

**Reduction in Terminal Follicles**

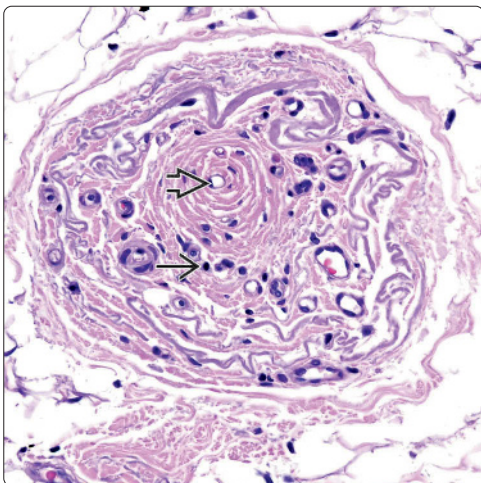


**Hair Fiber Diameter Diversity**

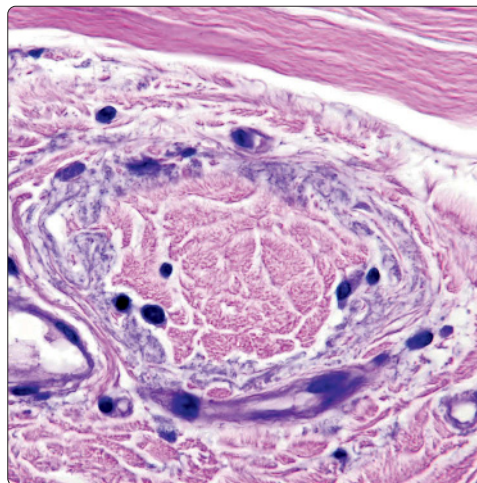


(Left) Horizontal section through the subcutaneous tissue highlights the reduction in terminal follicles and the diversity in hair follicle appearance [ ]. Stela [ ] mark sites of miniaturized follicles that lie higher in the dermis. (Right) Hair shafts [ ] are often lost during hematoxylin & eosin staining of horizontal sections. The resultant ovoid defects [ ] provide a rough gauge of hair fiber diameter and highlight the hair fiber diversity typical of AGA.

**Stela**



**Old Stela With Collagen Core**



(Left) This stela has a loose matrix with admixed blood vessels [ ] and sparse lymphocytes and mast cells [ ]. At this stage, medical therapy such as local androgen blockade may be successful. (Right) This older stela consists of a dense collagen core without blood vessels. At this stage, medical therapy is likely to be fruitless.



# Telogen Effluvium

## KEY FACTS

### TERMINOLOGY

- Nonscarring hair loss due to increased number of telogen follicles

### CLINICAL ISSUES

- Diffuse thinning of scalp hair, sometimes with bitemporal recession
- Patient may describe scalp pain (trichodynia)
- Hair loss may be inapparent to examiner
- History of external stressor 3 months prior to onset of hair loss

### MICROSCOPIC

- Increased telogen hairs (best evaluated in horizontal sections)
- Acute telogen effluvium (TE): > 20% telogen follicles
- Chronic TE: > 10% telogen follicles

### TOP DIFFERENTIAL DIAGNOSES

- Psychogenic pseudoeffluvium

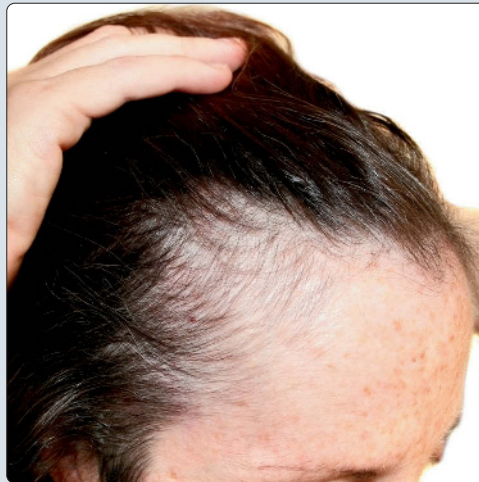
- Normal physical exam, pull test, hair wash test, and biopsy
- Androgenetic (pattern) alopecia
  - Hair loss in women most pronounced across top of scalp, with widened central part and preserved frontal hair line
  - Biopsy demonstrates follicles of diverse sizes and elastotic streamers beneath miniaturized vellus-like follicles
- Diffuse alopecia areata
  - Biopsy demonstrates peribulbar inflammation and miniaturized follicles overlying fibrovascular streamers containing melanophages, lymphocytes, and eosinophils

### DIAGNOSTIC CHECKLIST

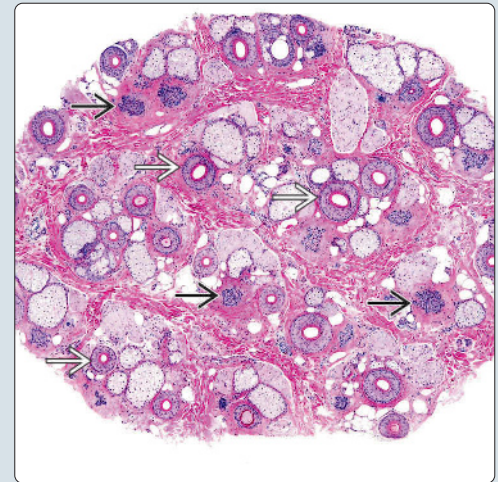
- TE is clinical diagnosis and rarely biopsied
- TE in recovery phase demonstrates normal number of telogen follicles

Temporal Recession

(Left) Temporal recession is a clue to telogen effluvium. Hair loss may also be diffuse and inapparent to the examining physician. (Courtesy A. Tauscher, MD.) (Right) Horizontal sections are best for evaluating telogen effluvium. This biopsy demonstrates 40% telogen follicles [box] and 60% anagen follicles [box].

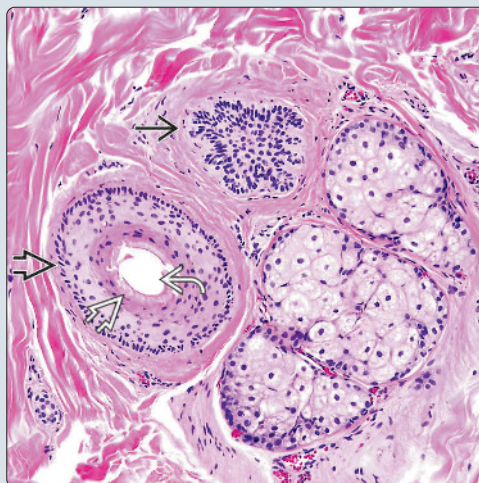


Increased Telogen Follicles

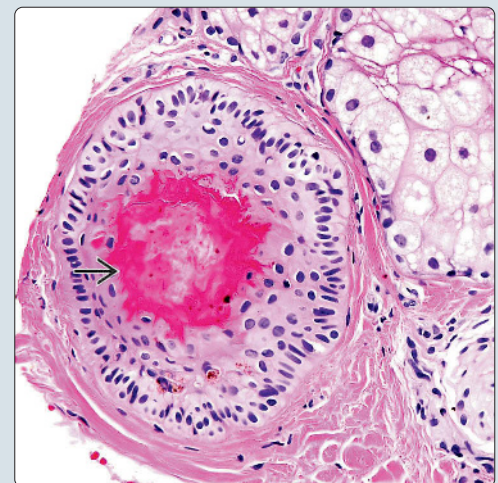


Late Telogen Follicle

(Left) A late telogen follicle [box] consists of a clump of basaloid cells with an irregular border like a splotch of ink. The adjacent anagen follicle [box] forms an inner root sheath [box] surrounding an empty canal [box] (the hair fiber was dislodged in processing). (Right) An early telogen follicle has a flaming red center [box].



Early Telogen Follicle



## TERMINOLOGY

### Abbreviations

- Telogen effluvium (TE)

### Definitions

- Nonscarring hair loss due to increased number of telogen hairs

## ETIOLOGY/PATHOGENESIS

### Acute Telogen Effluvium

- < 6 months duration
- External stressor precipitates telogen phase
- Causes include infection, parturition, pyrexia, trauma, and emotional stress

### Chronic Telogen Effluvium

- > 6 months duration
- Idiopathic in most cases
- May be due to iron deficiency, systemic diseases, malnutrition, or thyroid gland disease

## CLINICAL ISSUES

### Presentation

- Diffuse thinning of scalp hair, sometimes with bitemporal recession
- Patient may describe scalp pain (trichodynia)
- Hair loss may be inapparent to examiner
- History of external stressor 3 months prior to onset of hair loss

### Laboratory Tests

- Pull test
  - Physician grasps 40-60 hairs and applies gentle traction
  - Extraction of > 5 hairs indicates TE
- Hair wash test
  - Patient refrains from washing hair for 5 days, then soaps and rinses scalp in basin with drain lined by gauze
  - Shed hairs are collected and separated by length
  - If > 100 hairs shed, indicates TE
- Consider ferritin level, rapid plasma reagin (RPR) and thyroid stimulating hormone (TSH) assays as indicated by clinical context

### Treatment

- If external stressor can be identified, patient education and reassurance
- Careful drug history to uncover medication-induced telogen effluvium (e.g., oral contraceptives)
- In chronic TE, consider topical minoxidil

### Prognosis

- Acute TE: Full recovery expected
- Chronic TE: May last years

## MACROSCOPIC

### Examination of Shed or Pulled Hair Fibers

- Telogen (club) hairs have a depigmented bulb that can be identified with naked eye

## MICROSCOPIC

### Histologic Features

- Increased telogen hairs (best evaluated in horizontal sections)
- Acute TE: > 20% telogen follicles and > 66% terminal follicles
- Chronic TE: > 10% telogen follicles and > 66% terminal follicles

## DIFFERENTIAL DIAGNOSIS

### Psychogenic Pseudoeffluvium

- Patient has delusion of hair loss
- Normal physical exam, pull test, hair wash test, and biopsy
- May be sign of depression or body-dysmorphic disorder

### Androgenetic (Pattern) Alopecia

- Hair loss in women most pronounced across top of scalp, with widened central part and preserved frontal hair line
- Hair wash test reveals < 100 shed hairs, > 10% of which are < 3 cm in length (vellus-like hairs)
- Biopsy demonstrates follicles of diverse sizes and elastotic streamers beneath miniaturized vellus-like follicles

### Diffuse Alopecia Areata

- Scalp dermoscopy reveals tapered exclamation mark hairs and yellow dots corresponding to dilated empty follicular canals
- Biopsy demonstrates peribulbar inflammation and miniaturized follicles overlying fibrovascular streamers containing melanophages, lymphocytes, and eosinophils

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Clinical diagnosis and rarely biopsied; though common in the clinic, it is rare in laboratory
- Biopsy of recovering TE will look normal and will not show increased incidence of telogen hairs
- Both androgenetic alopecia and chronic alopecia areata will demonstrate increased telogen hairs that should not be misconstrued as TE

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## KEY FACTS

## TERMINOLOGY

- Self-inflicted hair plucking

## CLINICAL ISSUES

- Irregular patch of noninflammatory, incomplete hair loss over vertex or parietal scalp
- Eyebrows, upper eyelashes, and pubic hair may be involved
- Broken hairs produce stubbly-feeling scalp
- Negative pull test (gentle pulling of hair at edge of lesion yields few hairs)

## MICROSCOPIC

- Dilated follicular ostia containing melanin pigment casts and keratin debris
- Trichomalacia: Wavy, distorted lower follicular segment forming small, incompletely cornified hair fibers with variable pigmentation
- No deep inflammation
- Collapsed hair follicles devoid of hair fibers

- Erythrocytes within follicular epithelium or hair canal
- Signs of excoriation (scarring, lichenification, erosions)

## TOP DIFFERENTIAL DIAGNOSES

- Alopecia areata
  - Positive KOH preparation and fungal culture
- Tinea capitis
  - Peribulbar inflammation in acute phase and increased vellus-like follicles in chronic phase
- Traction alopecia
  - Histopathology similar to trichotillomania (TTM) though more vellus-like hairs and fewer pigment casts and trichomalacic hair fibers

## DIAGNOSTIC CHECKLIST

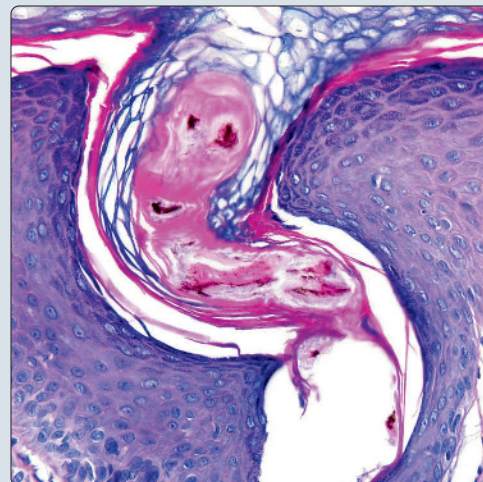
- Though pigment casts and trichomalacia suggest TTM, these may also be seen in alopecia areata
- Hair fibers often fall out of plane of section during processing of scalp biopsies; normal-shaped follicles without hair fiber should not be misinterpreted as TTM

## Poorly Circumscribed Patch of Hair Loss With Excoriation


**(Left)** Trichotillomania (TTM) clinically shows an irregular, poorly circumscribed patch of hair loss with signs of excoriation and some retained hairs across the crown of the scalp. (Courtesy B. Matthys, DO.) **(Right)** TTM histologically shows widened follicular ostium with a corkscrew shape containing soft keratin debris and demonstrating trichomalacia (small, dystrophic, and variably pigmented hair fibers).

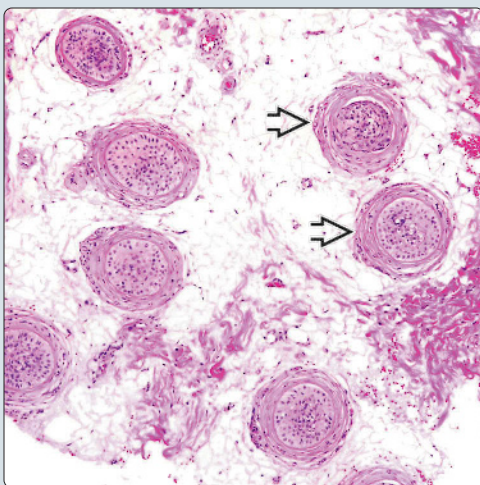


## Corkscrew Hairs

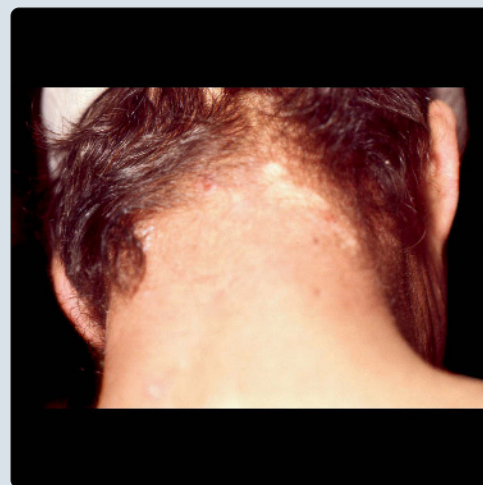


## Increased Catagen Hairs With Normal Follicular Density

**(Left)** A low-power view of a vertical section in the panniculus demonstrates increased catagen hairs  with normal follicular density. Note the absence of any deep inflammation, militating against alopecia areata. **(Right)** Photograph shows trichotillomania of the nuchal scalp with asymmetric angulated hair loss. Note sharp, well-defined borders with some hypopigmented scars and various hair lengths.



## Asymmetric Angulated Hair Loss



## TERMINOLOGY

### Abbreviations

- Trichotillomania (TTM)

### Definitions

- Self-inflicted hair plucking

## ETIOLOGY/PATHOGENESIS

### Forcible Extraction of Hairs by Patient

- Preschool children: Insecurity due to environmental stressors
- Adolescents: Impulse control disorder
- Older adults: Often linked to underlying psychiatric disorder such as depression

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - 0.6% lifetime prevalence
- Age
  - 5-12 years most commonly
- Sex
  - 85% female

### Presentation

- Irregular patch of noninflammatory, incomplete hair loss over vertex or parietal scalp
  - Eyebrows, upper eyelashes, and pubic hair may be involved
- Spares lower occiput, lower eyelashes
- Broken hairs produce stubbly-feeling scalp
- May be signs of excoriation
- Negative pull test (gentle pulling of hair at edge of lesion yields few hairs)

### Treatment

- Preschool children: Explanation and reassurance
  - More severe cases: Cognitive behavior therapy and clomipramine pharmacotherapy
- Adults: Treat any underlying psychiatric illness

### Prognosis

- Related to age of onset
  - Prior to age 7: Usually resolves spontaneously within 12 months
  - Adolescent/adult onset: Often chronic remitting-relapsing course

## MACROSCOPIC

### Dermoscopic Findings

- Blunt-ended broken hairs, black dots, hair fibers of variable length and caliber
- No exclamation mark hairs (useful in differentiating from alopecia areata)

## MICROSCOPIC

### Histologic Features

- Dilated follicular ostia containing melanin pigment casts and keratin debris

- Trichomalacia: Wavy, distorted lower follicular segment forming small, incompletely cornified hair fibers with variable pigmentation
- Collapsed hair follicles devoid of hair fibers
- Erythrocytes within follicular epithelium or hair canal
- Sparse inflammation (absolutely no deep inflammation)
- Signs of excoriation (scarring, lichenification, erosions)
- Increased numbers of non-inflamed catagen follicles

## DIFFERENTIAL DIAGNOSIS

### Alopecia Areata

- Primary consideration in differential
- Patches of hair loss are circular to oval, smooth to touch, more sharply demarcated, with positive hair pull test
- Peribulbar inflammation in acute phase and increased vellus-like follicles in chronic phase
- May occasionally see pigment casts and trichomalacia

### Tinea Capitis

- Scaling, sometimes pustular alopecia
- Positive KOH preparation and fungal culture
- Fungal arthroconidia either within (endothrix) or surrounding (ectothrix) hair fiber on biopsy

### Traction Alopecia

- Histopathology similar to TTM though more vellus-like hairs and fewer pigment casts and trichomalacic hair fibers
- Pattern of hair loss can be correlated with hair styling practices

### Congenital Triangular Alopecia

- Elongated triangular patches of alopecia across temporal scalp composed of vellus-like follicles on biopsy
- Often present at birth

### Tick Bite Alopecia

- Focal alopecia at site of tick bite
- Vellus-like follicles with inflammation centered on isthmus and hyperplasia of fibrous root sheath
- Tick may or may not be present

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Though pigment casts and trichomalacia suggest TTM, these may also be seen in alopecia areata
- Hair fibers often fall out of plane of section during processing of scalp biopsies; normal-shaped follicles without hair fiber should not be misinterpreted as TTM
- Histopathologic overlap with alopecia areata is sometimes greater in clinical practice than classically suggested, and correlation with clinical aspect is vital
- Follicular hemorrhage, catagen follicles, and relative paucity of inflammation favors TTM over alopecia areata
- Band-Aid sign: Normal regrowth of hair in area covered by bandage at follow-up of biopsy site

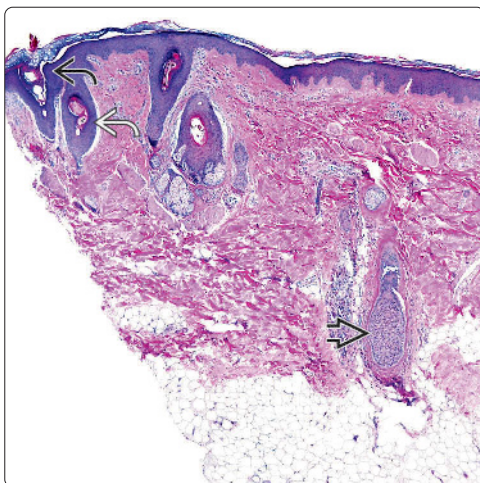
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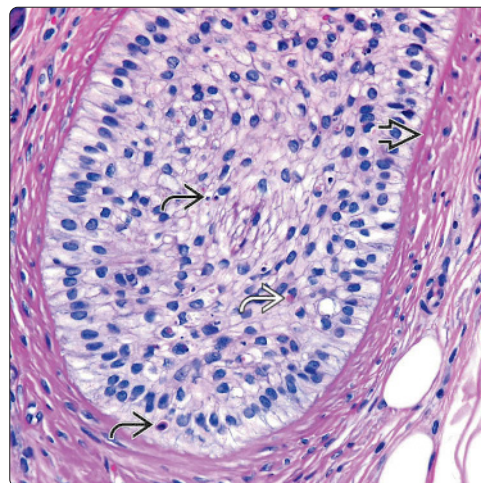


(Left) This vertical section demonstrates apparently reduced follicular density without scarring. There are no terminal follicles in the panniculus. The epidermis is slightly thickened and hyperkeratotic from excoriation. There are widened follicular ostia [X], twisted infundibula [X], and a catagen follicle [X]. (Right) Catagen follicles can be identified by apoptotic cells [X] and a thickened basement membrane [X]. Intraepithelial hemorrhage [X] is a clue to TTM.

Widened Follicular Ostia and Twisted Infundibula

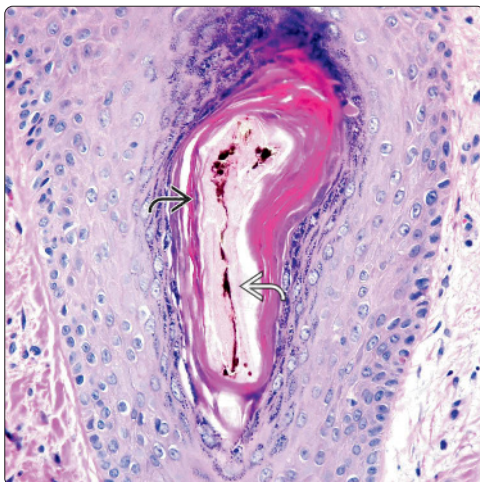


Catagen Follicle With Intraepithelial Hemorrhage

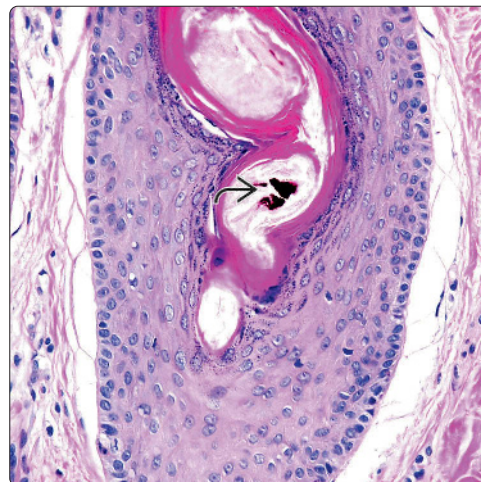


(Left) Trichomalacia and melanin pigment casts can be similar in appearance. Trichomalacia refers to the abnormal hair fibers formed by a damaged follicle, whereas a melanin pigment cast is a clump of melanin formed by melanocytes that have been uprooted from the bulb and stranded in the hair canal. This section demonstrates trichomalacia [X] because the collapsed hair cortex can still be recognized [X]. (Right) This is a pigment cast [X] because it consists of clumps of pigment.

Trichomalacia

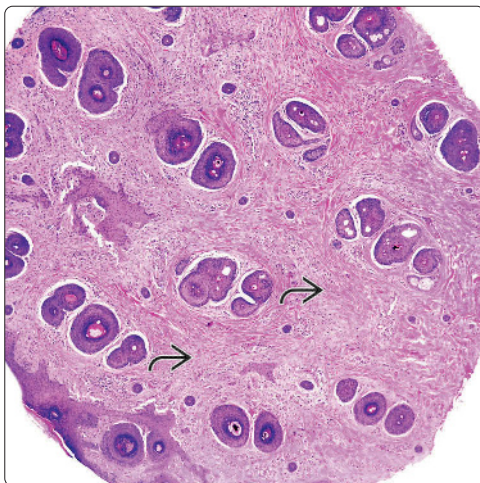


Pigment Cast

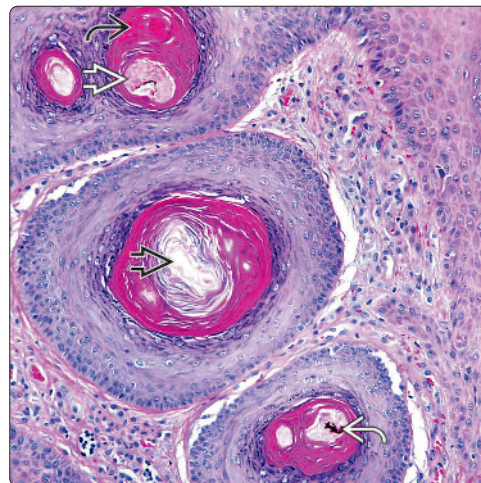


(Left) Horizontal sections through the upper follicle (infundibulum) demonstrate superficial scarring [X] from external trauma. Horizontal sections demonstrate the normal follicular density in TTM. The apparent reduction in follicular density in vertical sections is an illusion due to reduced anagen terminal follicles. (Right) Well-formed terminal hairs are absent [X]. The follicles are plugged with keratin [X], trichomalacic hair fibers [X], and melanin pigment casts [X].

Normal Follicular Density

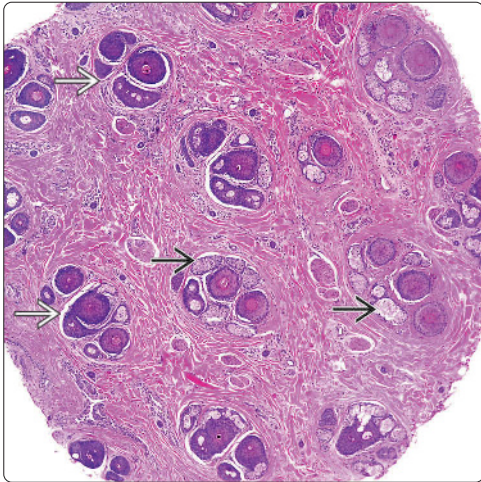


Trichomalacic Fibers and Pigment Casts

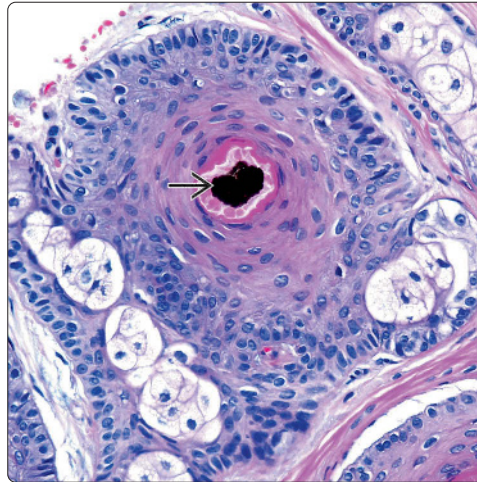




**Normal Hair Follicle Density**

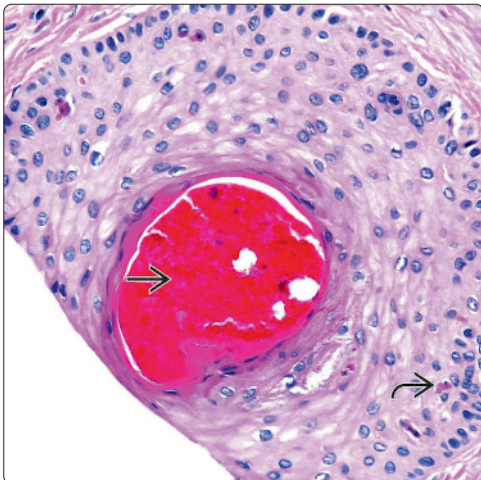


**Pigment Cast**

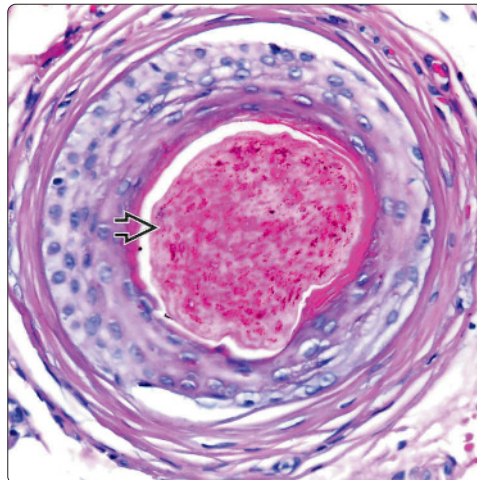


(Left) Follicles are normally grouped into units containing 2 to 4 follicles. Identifying evenly spaced clusters of 2 to 4 follicles in horizontal sections provides a shortcut to excluding cicatricial alopecia. Sebaceous glands are preserved, further militating against cicatricial alopecia. (Right) A well-formed pigment cast is shown within a partially collapsed follicle devoid of a hair fiber.

**Follicular Canal With Hemorrhage**

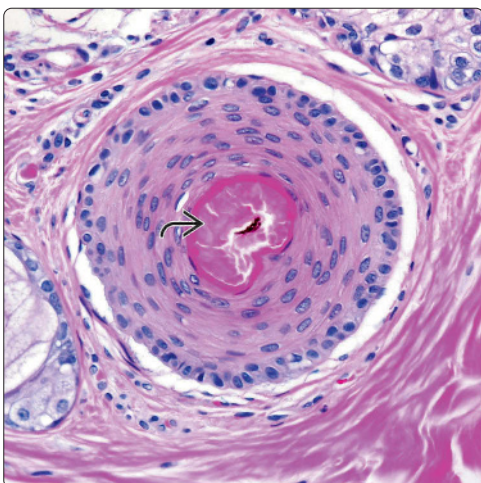


**Trichomalacia**

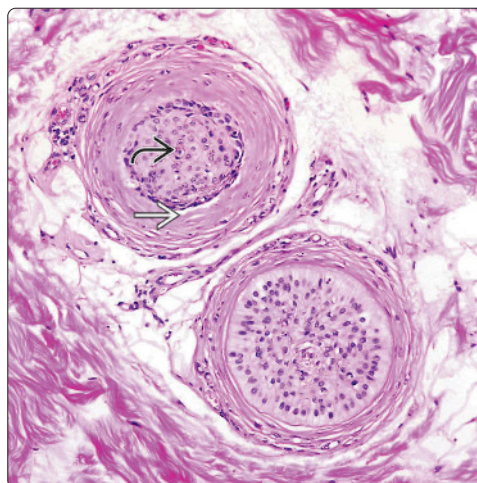


(Left) This follicular canal contains a pool of hemorrhage, a fairly specific sign of external trauma. There are a few apoptotic cells, suggesting this follicle is transitioning into catagen following the forcible avulsion of the hair fiber. (Right) Sometimes trichomalacia is subtle. This trichomalacic hair fiber has an irregular contour, slightly wavy core, and uneven melanin pigmentation.

**Collapsed Inner Root Sheath**



**Catagen Follicles**



(Left) It can be difficult to tell whether absence of hair fibers is real or an artifact of histology processing. The inner contour of the inner root sheath exactly matches the shape of the enclosed hair fiber. Collapsed, irregular inner root sheaths are a surrogate marker for genuine absence of a hair fiber. (Right) Catagen follicles are most easily seen in the panniculus. They can be identified by apoptotic cells and thickened basement membranes.



## Alopecia Areata

## KEY FACTS

## TERMINOLOGY

- Autoimmune nonscarring hair loss

## ETIOLOGY/PATHOGENESIS

- T cells and NK cells induce premature anagen arrest and involution

## CLINICAL ISSUES

- Oval or circular patches of complete hair loss
- All ages susceptible, but 60% of patients present prior to 20 years
- M:F ~ 1:1
- 90% of cases limited to scalp, though any hair-bearing skin susceptible

## MICROSCOPIC

- Acute phase
  - Peribulbar infiltrate of lymphocytes
  - Catagen/telogen follicles may outnumber anagen follicles

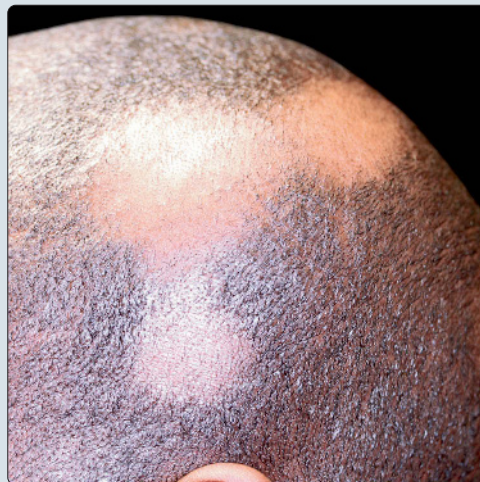
- Pigment casts in hair follicles
- Stelae with melanin and inflammation
- Dilated infundibula with laminated orthokeratin
- Chronic phase
  - Deep peribulbar inflammation absent
  - Equal numbers of terminal and vellus-like miniaturized follicles
  - May see peribulbar inflammation around miniaturized follicles
  - Nanogen follicles without hair fiber

## TOP DIFFERENTIAL DIAGNOSES

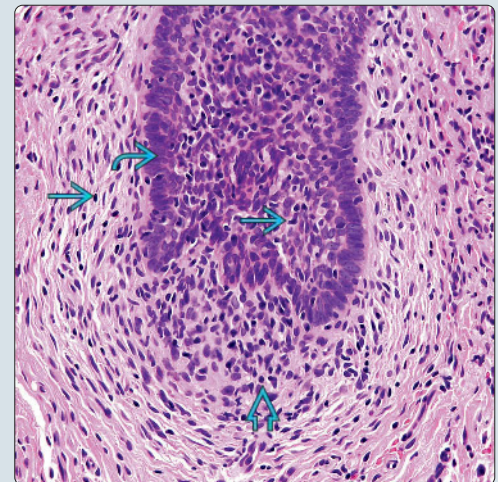
- Tinea capitis
- Trichotillomania
- Telogen effluvium
- Secondary syphilis
- Lupus erythematosus
- Androgenetic alopecia

Ovoid Patches of Hair Loss

(Left) Asymmetric ovoid and circular, noninflamed patches of hair loss are typical of alopecia areata (AA). (Courtesy T. Kestenbaum, MD.) (Right) AA shows lymphocytes that surround and infiltrate the bulb and papilla of the hair follicle. The distribution of inflammatory cells is referred to as a "swarm of bees."

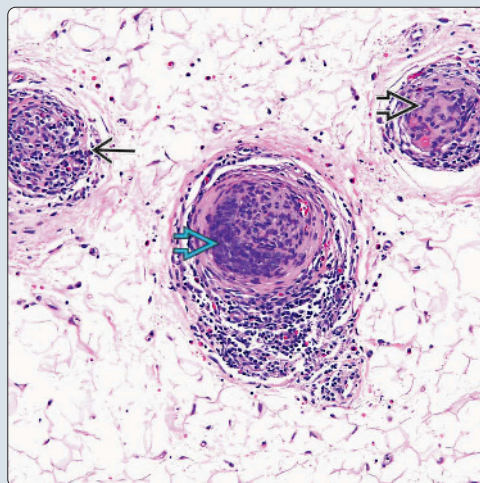


"Swarm of Bees" Surrounding Hair Bulb

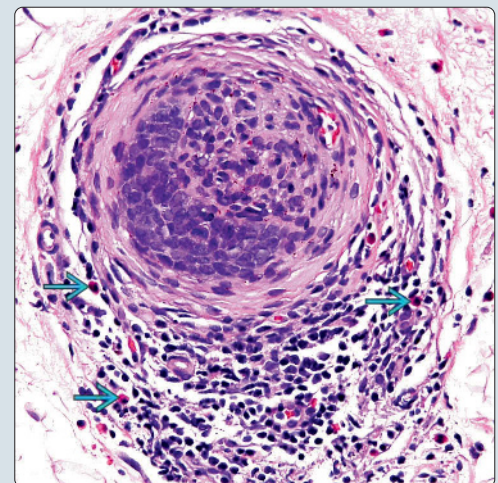


"Swarm of Bees" in Horizontal Section

(Left) Horizontal sections provide the greatest chance of capturing the peribulbar lymphocytic inflammation that typifies AA. Here, one sees an inflamed bulb, a mostly involuted follicular bulb, and an inflamed stela. These represent sequential stages in the inflammatory regression of hair follicles in AA. (Right) Higher magnification reveals a few admixed eosinophils.



Peribulbar Lymphocytic Infiltrate With Rare Eosinophils





## TERMINOLOGY

### Abbreviations

- Alopecia areata (AA)

### Definitions

- Autoimmune nonscarring hair loss

## ETIOLOGY/PATHOGENESIS

### Autoimmune

- Normal hair follicles do not express major histocompatibility complex (MHC) class I and II antigens
- In AA, induction of MHC class I antigens allows inflammatory reaction to follicular antigens
- CD4(+) T cells, CD8(+) T cells, and NK cells induce premature anagen arrest and involution

### Genetic

- Association with *HLA-DQ3* and twin-twin concordance studies suggest genetic predisposition

## CLINICAL ISSUES

### Epidemiology

- Age
  - All ages susceptible, but 60% of patients present prior to 20 years
- Sex
  - M:F ~ 1:1

### Site

- 90% of cases limited to scalp, though any hair-bearing skin susceptible

### Presentation

- Oval or circular patches of complete, otherwise asymptomatic hair loss (patchy alopecia)
- Diffuse thinning of scalp hair (diffuse AA)
- Loss of all scalp hair (alopecia totalis)
- Loss of all scalp and body hair (alopecia universalis)

### Treatment

- Drugs
  - Topical corticosteroids (children) and intralesional corticosteroids (adults)

### Prognosis

- Likelihood of hair regrowth corresponds to extent of hair loss
  - 50% of patients with patchy alopecia have complete recovery within 1 year
  - 10% of patients with total or universal alopecia have complete hair regrowth

## MACROSCOPIC

### Dermoscopic Findings

- Active disease
  - Yellow dots: Dilated infundibula containing keratin and sebum
  - Short terminal hairs with narrowing at attachment to scalp ("exclamation mark hairs")

- Normal-sized terminal hairs with narrowing at attachment to scalp ("coudability hairs")
- Black dots: Remnants of broken and tapered hairs
- Remitting disease
  - Yellow dots
  - Clusters of short vellus hairs

## MICROSCOPIC

### Histologic Features

- Acute phase
  - Peribulbar infiltrate of lymphocytes and rare eosinophils ("swarm of bees")
  - Dyskeratosis, pyknosis, spongiosis of matrical epithelium
  - Catagen/telogen follicles may outnumber anagen follicles
  - Melanin pigment casts in hair follicles
  - Dilated infundibula with laminated orthokeratin (dermoscopic yellow dots)
  - Stelae (columns of vascularized connective tissue) with melanin and inflammatory cells beneath involuting follicles
- Chronic phase
  - Deep peribulbar inflammation absent
  - Equal numbers of terminal and vellus-like miniaturized hairs
  - Equal numbers of telogen, anagen follicles
  - Angiofibrotic stelae beneath miniaturized follicles
  - Nanogen follicles without hair fiber

## DIFFERENTIAL DIAGNOSIS

### Children

- Tinea capitis
  - Signs of inflammation and scaling by physical exam
  - Fungal arthroconidia within follicles/hairs on biopsy
- Trichotillomania
  - Irregular patches with rougher surface containing broken hairs of different lengths

### Adults

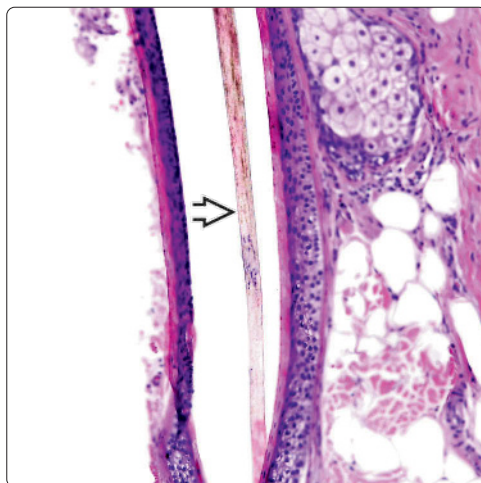
- Trichotillomania
  - Noninflammatory biopsy with trichomalacia
- Telogen effluvium
  - Telogen hairs by pull test, no miniaturization or inflammation on biopsy
- Secondary syphilis
  - Moth-eaten alopecia with plasma cells, positive rapid plasma reagin
- Lupus erythematosus
  - Symptomatic focal alopecia with scarring, mucin on biopsy

## SELECTED REFERENCES

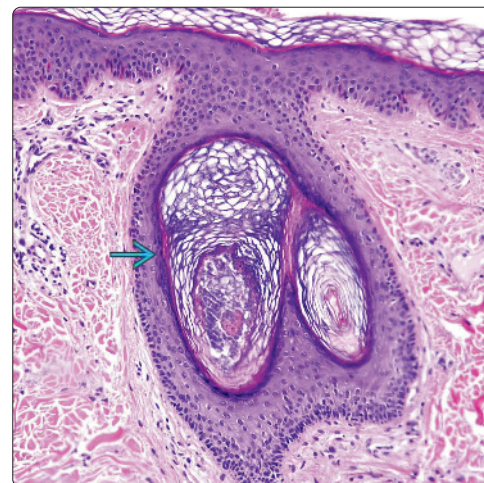
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2. Yoon TY et al: Diagnostic usefulness of a peribulbar eosinophilic infiltrate in alopecia areata. *JAMA Dermatol.* 150(9):952-6, 2014
3. Alkhalifah A et al: Alopecia areata update: part I. Clinical picture, histopathology, and pathogenesis. *J Am Acad Dermatol.* 62(2):177-88, quiz 189-90, 2010

(Left) An "exclamation mark" hair consists of a hair fiber that tapers in diameter proximally and exhibits diminished proximal pigmentation. When examined clinically, these hairs appear to float on the surface of the skin because they are narrowed and hypopigmented at the point of exit from the skin surface. (Right) Dilated follicular ostia containing laminated keratin with bacterial and sebaceous debris can be identified in vertical sections and produce "yellow dots" on dermoscopy.

"Exclamation Mark" Hair

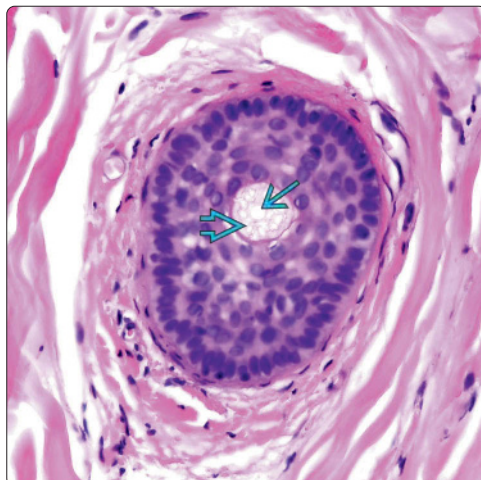


Dilated Follicles With Laminated Keratin

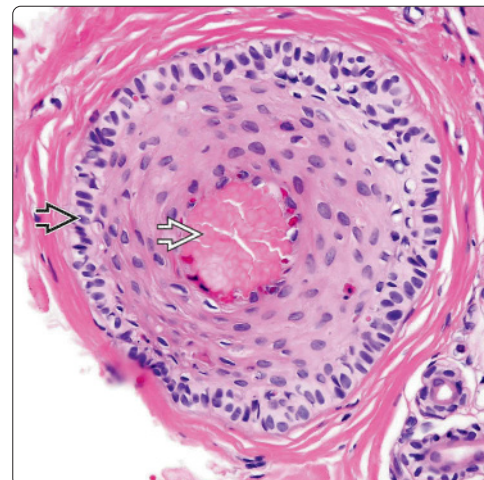


(Left) If the hair fiber is smaller in diameter than the thickness of the corresponding inner root sheath, it is considered a vellus or vellus-like hair. Increased numbers of these miniaturized hairs suggest either AA or androgenetic alopecia. (Right) In chronic AA, follicles may fail to produce a hair fiber. Nanogen follicles form a solid core of inner root sheath protein without a hair fiber.

Vellus Hair

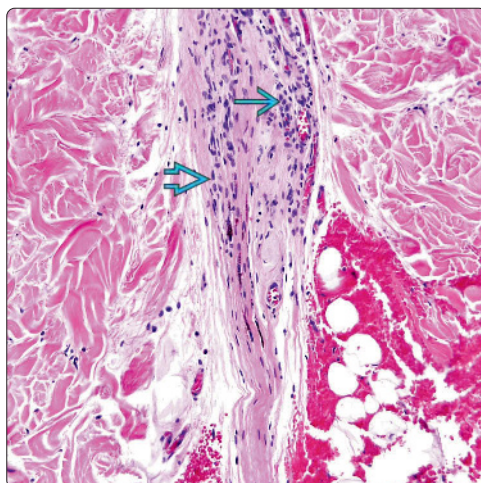


Nanogen Follicle

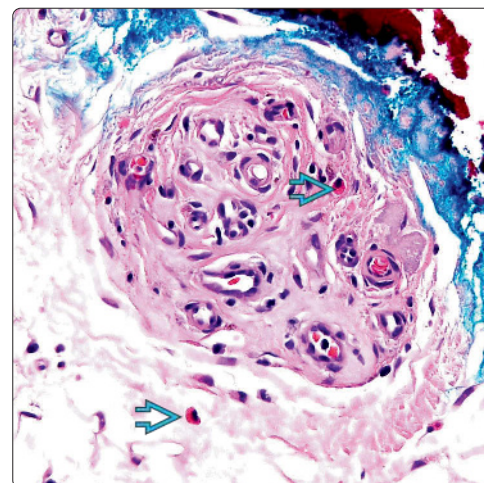


(Left) Follicular stela may be few and easily overlooked in vertical sections. This example contains scattered lymphocytes. Follicular stela in androgenetic alopecia and telogen follicles do not contain lymphocytes. (Right) In horizontal sections, follicular stela appear as transected fibrovascular cylinders. In addition to lymphocytes, eosinophils within these stela provide a useful clue to AA.

Stelae in Vertical Section

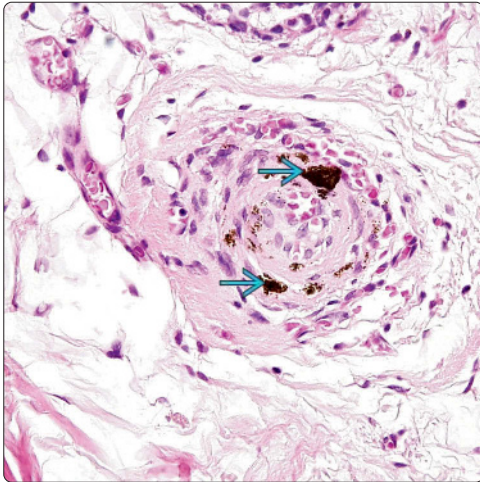


Stelae in Horizontal Section

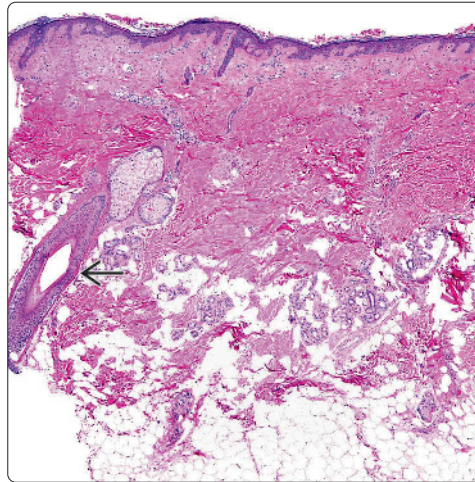






**Clumps of Melanin Pigment in Stela**

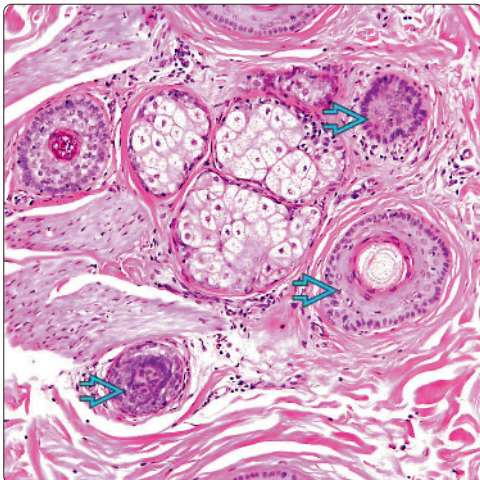


**Reduced Number of Hair Follicles**






**(Left)** Over time, inflammation and vascularity in the stela diminish and the collagen content increases. Clumps of melanin pigment  in the stela may persist and also provide a helpful clue to AA. **(Right)** In this vertically sectioned trephine punch biopsy, terminal hairs  are greatly diminished, and the skin might be mistaken for that of the trunk or an extremity. Note the absence of solar elastosis. This suggests an acute rather than chronic hair loss.

**Miniaturization of Follicles**

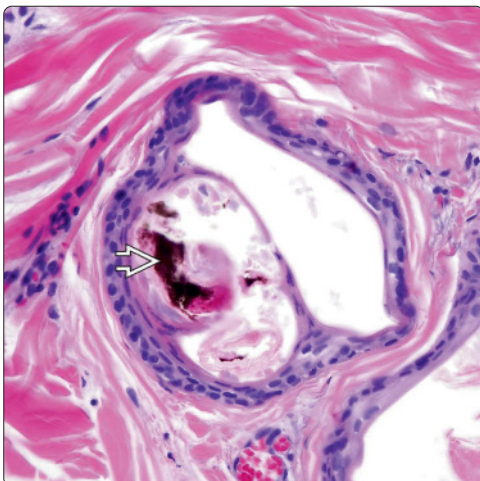


**Melanin Pigment in Hair Follicles**

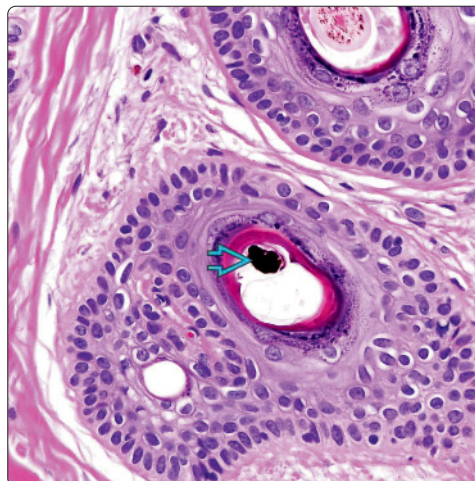




**(Left)** In normal scalp, the terminal:vellus follicle ratio is 7:1. The progressive miniaturization of follicles  in chronic AA shifts this ratio toward indeterminate-sized and vellus-like follicles. **(Right)** The result of nanogen pilogenesis is an amorphous glob of soft keratin  and melanin pigment  within the follicular ostium. These may be misinterpreted as the pigment casts or distorted hair fibers (trichomalacia) of trichotillomania.

**Pigment Within Follicular Canal**



**Melanin Globules in AA**



**(Left)** Rarely, pigment clumps  can be seen within the follicular canals in AA, prompting confusion with trichotillomania. **(Right)** Though commonly associated with trichotillomania, melanin globules  may also be encountered in AA.



# Lichen Planopilaris

## KEY FACTS

### TERMINOLOGY

- Follicular lichen planus

### CLINICAL ISSUES

- Cicatricial alopecia that mainly affects women at vertex scalp in multifocal manner presenting as itchy perifollicular erythema, hyperkeratotic perifollicular scale involving periphery or margin of area of scarring on scalp
- 3 variants exist
  - Classic lichen planopilaris (LPP) (which can be seen with skin and mucosal findings of lichen planus)
  - Graham-Little syndrome
  - Frontal fibrosing alopecia

### MICROSCOPIC

- Dense lichenoid infiltrate of mainly lymphocytes involving basal keratinocytes of infundibular portion of follicle apparatus
- Interfollicular epidermis is typically uninvolved

- Overlying hyperkeratosis is not uncommon
- Early findings
  - Focal lymphoid aggregates
  - Perifollicular mucinous fibrosis primarily around infundibulum
- Late findings
  - Dense infiltrate of lymphocytes sometimes with associated cytoid bodies
  - May lose classical features due to scarring of dermis
    - Loss of follicles and loss of adnexal structures

### TOP DIFFERENTIAL DIAGNOSES

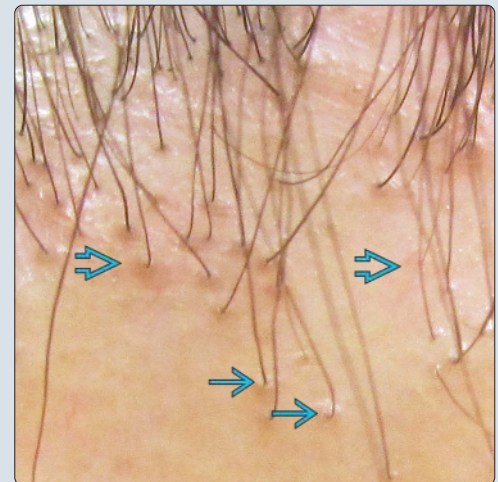
- Discoid lupus erythematosus
- Pseudopelade of Brocq
- Central centrifugal cicatricial alopecia

#### Perifollicular Erythema

(Left) Perifollicular erythema with some associated scale in a patch of alopecia is shown. (Courtesy K. Huang, MD.) (Right) Closeup view shows perifollicular scale and erythema. (Courtesy K. Huang, MD.)

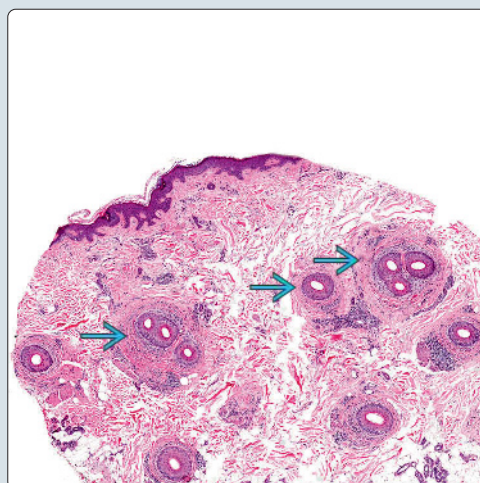


#### Lichen Planopilaris

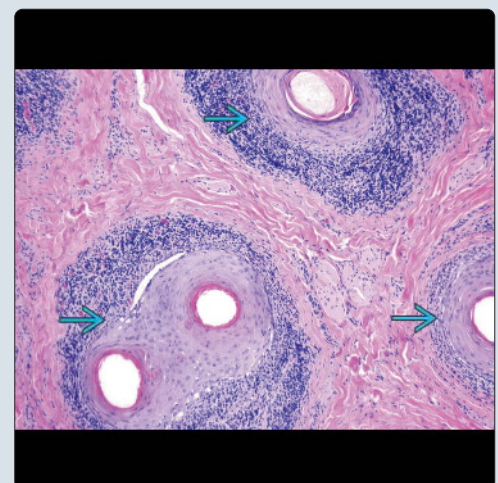


#### Perifollicular Fibrosis and Scarring

(Left) H&E shows advanced stage of lichen planopilaris with increased perifollicular fibrosis and scarring. (Right) Higher power image shows interface dermatitis involving follicular epithelium. (Courtesy L. Cohen, MD.)



#### Interface Dermatitis





## TERMINOLOGY

### Abbreviations

- Lichen planopilaris (LPP)

### Synonyms

- Follicular lichen planus
- Scarring alopecia

### Definitions

- Lichenoid interface dermatitis affecting epidermis of hair follicle

## CLINICAL ISSUES

### Epidemiology

- Sex
  - Mainly affects women (> 75%)

### Site

- Affects vertex of scalp

### Presentation

- Cicatricial alopecia that mainly affects women at vertex scalp in multifocal manner presenting as itchy perifollicular erythema, hyperkeratotic perifollicular scale involving periphery or margin of area of scarring on scalp
- Occasionally tufting of hairs can be seen as well as single, lone hair follicles
- 3 variants exist
  - Classic LPP (which can be seen with skin and mucosal findings of lichen planus)
  - Graham-Little syndrome (triad of 3 features)
    - Progressive multifocal cicatricial scalp alopecia
    - Nonscarring alopecia of hair in axilla and groin
    - Keratosis pilaris on trunk or extremities
  - Frontal fibrosing alopecia
    - Primarily affects postmenopausal women on front of their scalp in moth-eaten appearance

### Treatment

- Options, risks, complications
  - Treatments options include immunosuppressants, antibiotics (tetracyclines) and antimalarials
  - However, treatment often fails to fully control slow progression of hair loss

### Prognosis

- Slowly progressive and can sometimes stabilize or become quiescent

## MICROSCOPIC

### Histologic Features

- Dense lichenoid infiltrate of lymphocytes with few admixed macrophages involving basal layer of follicular epithelium at level of infundibulum
- Interfollicular epidermis is typically uninvolved
- Overlying hyperkeratosis is not uncommon
- Early findings
  - Focal lymphoid aggregates
  - Perifollicular mucinous fibrosis primarily around infundibulum

- Late findings
  - Dense infiltrate of lymphocytes sometimes with associated cytooid bodies
  - May lose classical features due to scarring of dermis
    - Loss of follicles and loss of adnexal structures

## ANCILLARY TESTS

### Immunofluorescence

- Direct Immunofluorescence (DIF)
  - Usually negative in early lesions, but can demonstrate IgM, IgG positivity of fibrin and cytooid bodies
  - Helpful in distinguishing between DLE (linear DE junction activity) versus LPP (globules intermittently at DE junction)

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Discoid lupus erythematosus (more adnexal involvement compared to LPP)
  - Hyperkeratosis, follicular plugging, thickened basement membrane, vacuolar degeneration of basal keratinocytes, periadnexal lymphoid aggregates, DIF positive IgG, C3, IgM, IgA, C1q
- Pseudopelade of Brocq
  - Thickened elastic fibers of dermis, broad fibrous tract remnants
- Central centrifugal cicatricial alopecia
  - Concentric lamellar fibroplasia of remaining follicles

### Clinical

- Discoid lupus erythematosus
  - Frequently has follicular plugging, telangiectasias, mottled pigmentation and atrophy
- Pseudopelade of Brocq
  - Tends to appear as smooth areas of scarring alopecia without hyperkeratosis or erythema
- Central centrifugal cicatricial alopecia
  - Occurs on central scalp or vertex as ill-defined scarring alopecia that gradually expands

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Perifollicular erythema and scale

### Pathologic Interpretation Pearls

- Predominantly infundibular involvement with lichenoid infiltrate vs. isthmus as seen in DLE
- DIF can aid in differentiating LPP (nonlinear pattern at DE junction) and DLE (linear)

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**Lone Single Follicles**

(Left) Vertex scalp with scarring alopecia exhibits lone, single follicles along the periphery of the active margin. (Courtesy A. Lipworth, MD.) (Right) Closeup view shows the remaining few follicles within a scarred area of scalp lacking follicular ostia. (Courtesy A. Lipworth, MD.)

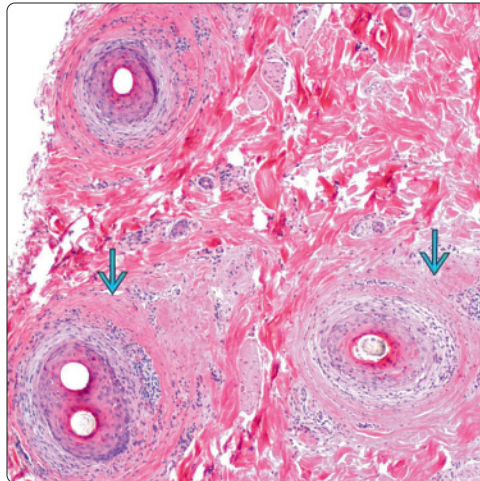


**Follicle Lacking Follicular Ostia**

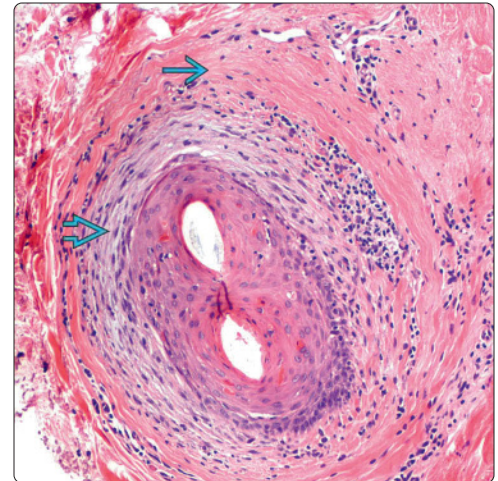


**Perifollicular Fibrosis**

(Left) Higher power image shows perifollicular fibrosis and scarring. (Right) High-power image shows perifollicular mucin and fibrosis.

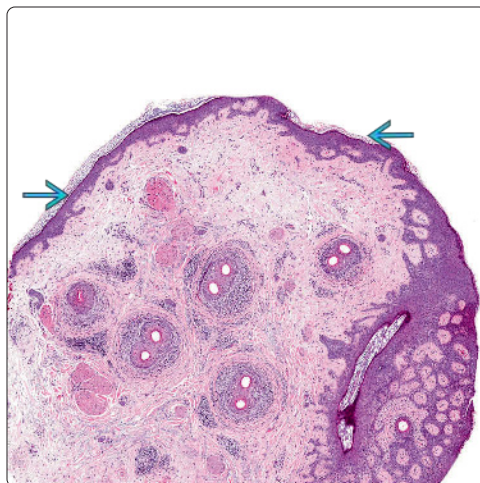


**Perifollicular Mucin and Fibrosis**

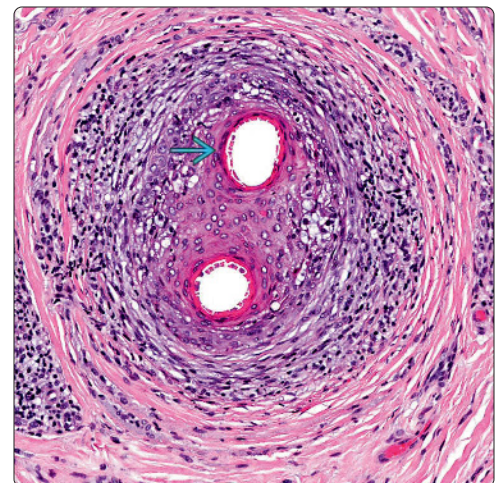


**Lack of Interfollicular Epidermal Involvement**

(Left) Oblique section demonstrates lack of interfollicular epidermal involvement. (Right) High-power view shows a follicle being obliterated by the dense lichenoid infiltrate.

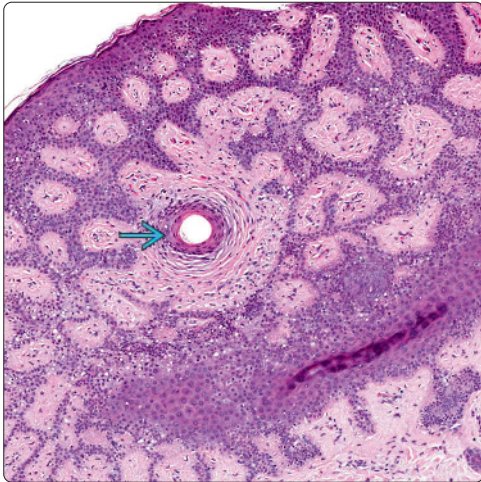


**Obliteration of Follicle by Dense Lichenoid Infiltrate**

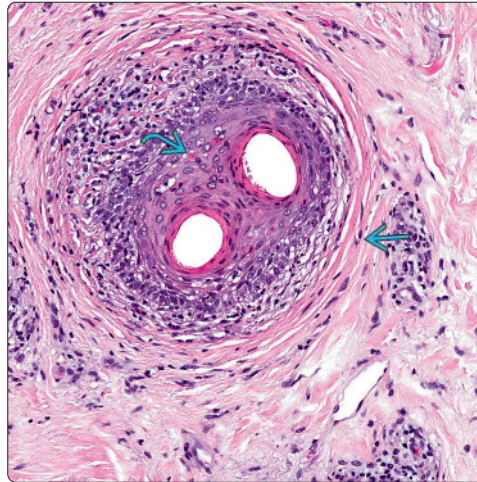




**Perifollicular Fibrosis at Level of Infundibulum**

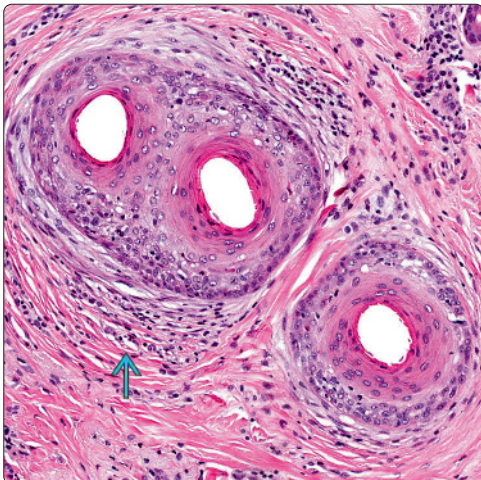


**Perifollicular Fibrosis With Dyskeratotic Keratinocytes**

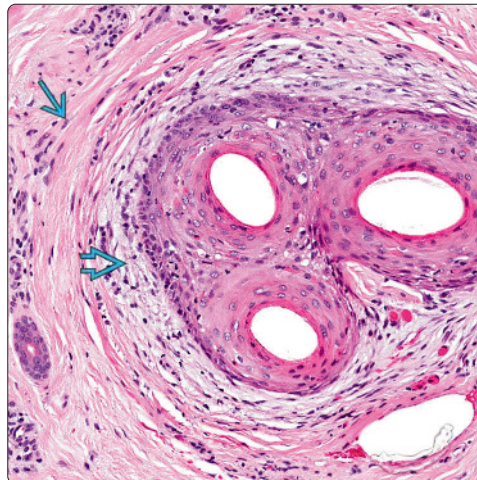


(Left) Another oblique section demonstrates perifollicular fibrosis at the level of the infundibulum [1]. (Right) H&E shows perifollicular fibrosis [2] as well as a lichenoid infiltrate with dyskeratotic keratinocytes [3].

**Compound Follicle With Loss of Sebaceous Glands**

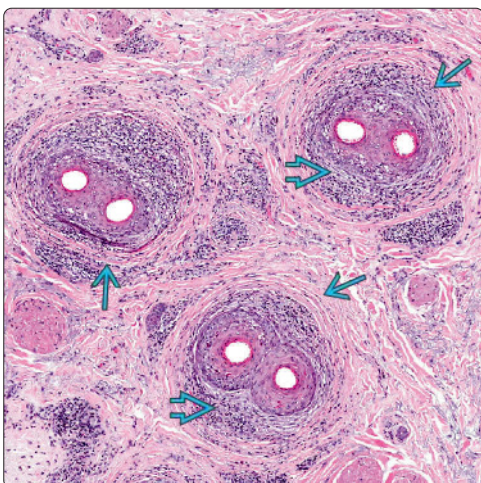


**Absent Sebaceous Glands With Perifollicular Mucin and Fibrosis**

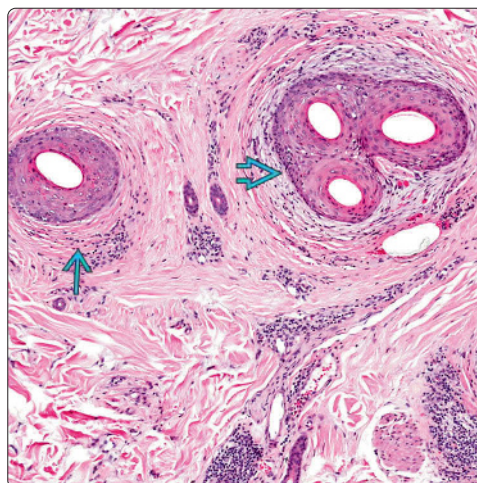


(Left) H&E shows perifollicular fibrosis [1] around a compound follicle with a complete absence of sebaceous glands indicative of a scarring alopecia. (Right) H&E shows perifollicular mucin [2] and fibrosis [3] around another compound follicle with complete loss of sebaceous glands.

**Lichenoid Infiltrate With Perifollicular Fibrosis**



**Mucin and Fibrosis**



(Left) H&E shows perifollicular mucin [1] and fibrosis [2] with a lichenoid infiltrate surrounding compound hair follicles without sebaceous glands. (Right) H&E shows perifollicular mucin [1] and fibrosis [2].



# Discoid Lupus Alopecia

## KEY FACTS

### ETIOLOGY/PATHOGENESIS

- Scarring and permanent hair loss thought to be due to inflammation of bulge region leading to destruction of follicular stem cells

### CLINICAL ISSUES

- Erythematous, scaly papules coalesce into irregular plaques, later becoming atrophic with follicular plugging and adherent scales (carpet tack sign)
- Old lesions heal with scarring, telangiectasia, and pigmentary alteration

### MICROSCOPIC

- Features evolve with age of lesion; highest yield when biopsy is taken from mature, well-established lesion with few remaining follicles
  - Vacuolar, or lichenoid (less common) interface dermatitis with marked hydropic degeneration and pigment incontinence

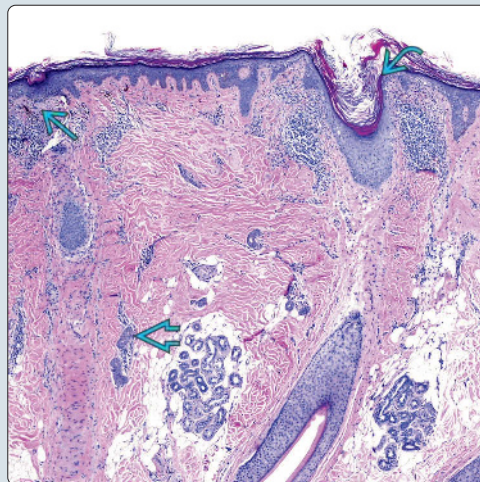
- Variably dense perivascular and periadnexal lymphoplasmacytic infiltrate in superficial and deep dermis
- Infiltrate is predominantly at level of follicular isthmus
- Late lesions may show prominent follicular plugging and diffuse dermal scarring with loss of pilosebaceous units

### TOP DIFFERENTIAL DIAGNOSES

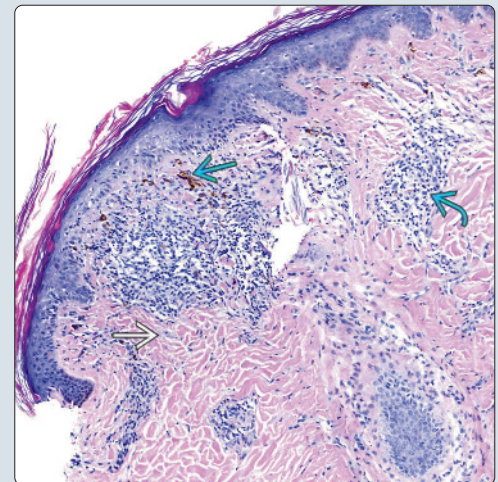
- Lichen planopilaris
  - Lichenoid (but not vacuolar) dermatitis with "skip," or uninvolved, areas between hair follicles
  - Inflammation is centered higher, at level of infundibulum
  - Results in wedge-shaped scars rather than throughout dermis
  - Absent: Basement membrane thickening, dermal mucin, involvement of eccrine glands and coil

**Follicular Plugging and Interface Dermatitis**

(Left) This low-magnification view shows follicular plugging and interface dermatitis. Perieccrine and perivascular inflammation is typically not present in lichen planopilaris. (Right) Vacuolar interface dermatitis is identified along with prominent pigment incontinence. Note also the perivascular inflammation and dermal mucin.

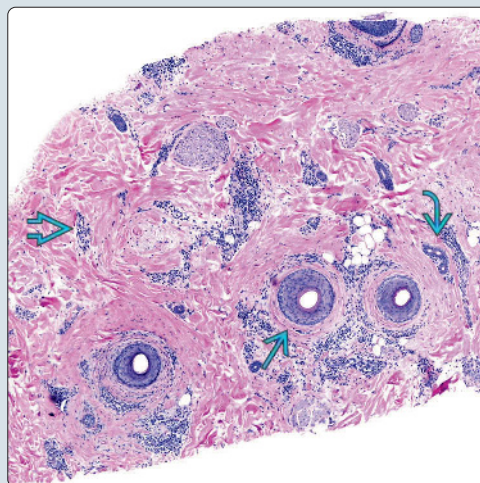


**Interface Dermatitis With Pigment Incontinence**

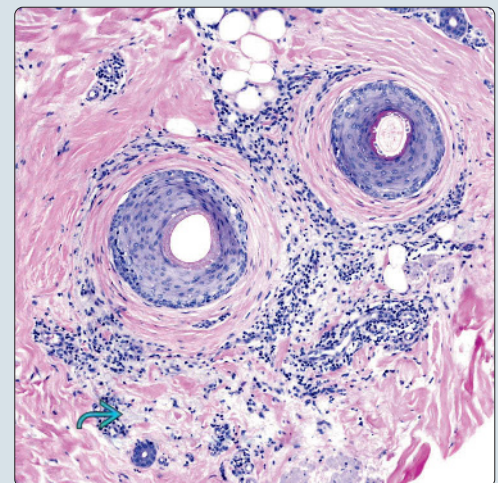


**Decreased Follicles With Perifollicular Fibrosis**

(Left) Transverse sections show a decreased number of follicles, as well as surrounding fibrosis and inflammation. Note the absence of sebaceous lobules and perieccrine as well as perivascular inflammation. (Right) On transverse sections, discoid lupus alopecia will show perifollicular fibrosis and inflammation. Note the absence of sebaceous lobules and presence of interstitial mucin. The presence of mucin favors discoid lupus erythematosus over other scarring alopecias such as lichen planopilaris.



**Perifollicular Fibrosis With Absent Sebaceous Glands**





## TERMINOLOGY

### Abbreviations

- Discoid lupus erythematosus (DLE)

### Synonyms

- Discoid alopecia of chronic cutaneous lupus erythematosus

### Definitions

- Permanent, scarring alopecia characterized by vacuolar interface dermatitis

## ETIOLOGY/PATHOGENESIS

### Precise Cause Unknown

- Scarring and permanent hair loss thought to be due to inflammation of bulge region leading to destruction of follicular stem cells

## CLINICAL ISSUES

### Presentation

- Early: Erythematous, scaly papules that coalesce into irregularly shaped plaques favoring face and scalp
- Later becomes atrophic with follicular plugging and adherent scales
  - Carpet tack sign: When scale is lifted, there are keratotic spikes on underside
- Old lesions heal with scarring, telangiectasia, and hypo- or hyperpigmentation
- May occur as lesions of chronic cutaneous lupus without systemic involvement (most common) or as manifestation of systemic lupus
- < 10% of patients with discoid lupus develop systemic lupus symptoms

### Treatment

- Topical and intralesional corticosteroids; topical nonsteroidal immunomodulators such as tacrolimus and pimecrolimus; oral antimalarials, systemic steroids
- 2nd-line agents include oral retinoids, methotrexate, thalidomide, and other systemic immunomodulatory medications
- Protection from sun is important, as sunlight is known trigger

### Prognosis

- Once scarring develops, resulting alopecia is permanent

## MICROSCOPIC

### Histologic Features

- Features evolve with age of lesion; highest yield when biopsy is taken from mature, well-established lesion with few remaining follicles
  - Vacuolar, or lichenoid (less common) interface dermatitis usually with marked hydropic degeneration and pigment incontinence
    - Cytooid bodies may be seen
  - Basement membrane thickening (highlighted by PAS stain)
  - Hyperkeratosis, follicular plugging; epidermis is usually atrophic but may be acanthotic

- Variably dense perivascular and periadnexal lymphoplasmacytic infiltrate in superficial and deep dermis
  - Infiltrate is predominantly at level of follicular isthmus
- Increased deep dermal mucin is often, but not always, noted
- Early lesions may only show mild perifollicular fibrosis and focal interface dermatitis
- Late lesions may show prominent follicular plugging and diffuse dermal scarring with loss of pilosebaceous units
  - Scarring throughout dermis may be highlighted by elastic tissue stain such as Verhoeff-van Gieson

## ANCILLARY TESTS

### Immunofluorescence

- Direct immunofluorescence should be performed on well-established lesion to avoid false-negative results
- Granular band of IgG, IgA, IgM, and C3 at follicular basement membrane zone

## DIFFERENTIAL DIAGNOSIS

### Lichen Planopilaris

- Lichenoid (but not vacuolar) dermatitis with "skip," or uninvolved, areas between hair follicles
- Inflammation is centered higher, at level of infundibulum
- Absent: Basement membrane thickening, dermal mucin, involvement of eccrine glands and coil
- Colloid bodies are more frequent and may fill fibrous tracts
- Results in wedge-shaped scars rather than throughout dermis
- DIF is either negative or demonstrates shaggy fibrin and cytooid bodies

### Alopecia Areata

- DLE can cause severe shift to catagen and telogen phases and deep inflammation, which can mimic alopecia areata

### Late Stages of All Cicatricial Alopecias Are Essentially Indistinguishable

- Includes lichen planopilaris, central centrifugal cicatricial alopecia, and pseudopelade

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# Central Centrifugal Cicatricial Alopecia

## KEY FACTS

### ETIOLOGY/PATHOGENESIS

- Associated with traction hair styles (braids, weaves, extensions)
- Destruction of hair follicle stem cells in follicular bulge produces permanent alopecia

### CLINICAL ISSUES

- Single, steadily expanding, circular plaque of alopecia across vertex of African American women

### MICROSCOPIC

- Sparse lymphohistiocytic perifolliculitis
- Myxoid concentric/hourglass fibrosis of upper hair follicle segment
- Eccentric atrophy of outer root sheath
- Premature desquamation of inner root sheath, often in upper panniculus or lower dermis
- Atrophic dermis with narrow, horizontally arranged collagen bundles

- Elastic fibers preserved between atrophic collagen bundles
- Broad fibrous scars devoid of elastic fibers located at sites of previous follicles
- Hair fiber foreign body granulomas

### TOP DIFFERENTIAL DIAGNOSES

- Follicular lichen planus (lichen planopilaris)
  - Biopsy demonstrates lichenoid inflammation of upper follicle with squamatization, hypergranulosis, superficial wedge-shaped scars devoid of elastic fibers
- Lupus erythematosus
  - Biopsy demonstrates epidermal atrophy, vacuolar interface dermatitis, scale, follicular plugging, superficial and deep perivascular inflammation
- Brocq pseudopelade
- Androgenetic (pattern) alopecia

### DIAGNOSTIC CHECKLIST

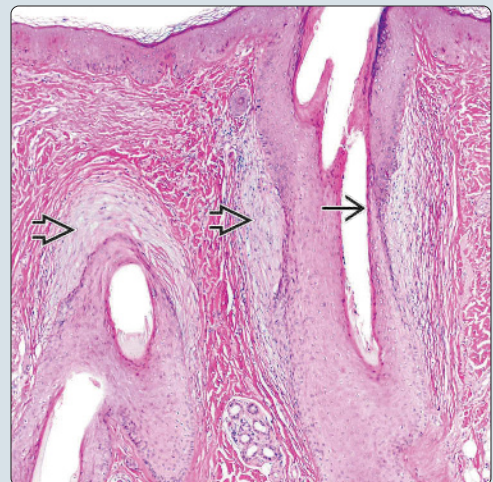
- Premature desquamation of inner root sheath may be seen in other scarring alopecias

Patch of Alopecia on Central Scalp

(Left) Central centrifugal cicatricial alopecia (CCCA) presents as a single patch of noninflammatory alopecia across the central scalp of an African American woman. (Courtesy M. Mahan, MD.) (Right) Early CCCA demonstrates myxoid hourglass fibrosis with eccentric thinning of the follicular wall, loss of sebaceous glands, and sparse lymphohistiocytic perifolliculitis.

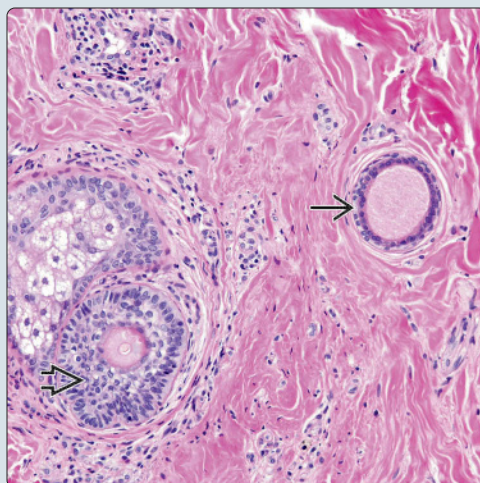


Hourglass Fibrosis With Eccentric Thinning

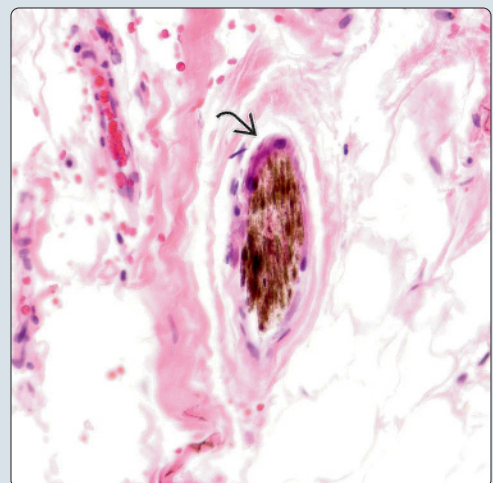


Dilated Eccrine Ducts and Spared Vellus Hairs

(Left) Vellus hairs are often spared in early CCCA. Eccrine ducts are often dilated in cicatricial alopecias of all sorts, perhaps due to the mechanical stretching effect of a shrunken dermis. (Right) Another finding of early CCCA is naked hair shafts surrounded by foreign body giant cells.



Giant Cells Reacting to Naked Hair Shaft





## TERMINOLOGY

### Abbreviations

- Central centrifugal cicatricial alopecia (CCCA)

### Synonyms

- Follicular degeneration syndrome, hot comb alopecia

### Definitions

- Lymphocytic scarring alopecia across vertex mostly seen in adult African American women

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- Associated with traction hair styles (braids, weaves, extensions)
- Prolonged traction or traumatic hair styling induces folliculitis and loss of immune privilege among hair follicle stem cells
- Destruction of hair follicle stem cells in follicular bulge produces permanent alopecia

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - 17% of African American women
- Age
  - Mean age of 58 years

### Site

- Vertex/crown of scalp

### Presentation

- Insidious onset of single, steadily expanding, circular plaque of alopecia
- Involved skin is supple, flesh-toned, and lacks visible follicular ostia, erythema, pustules, or follicular hyperkeratosis

### Treatment

- Surgical approaches
  - In end-stage disease, hair transplantation can be considered
- Drugs
  - Topical and intralesional corticosteroids
  - Oral antibiotics (tetracycline, doxycycline)

### Prognosis

- Although some authors report success with medical therapy, CCCA is often resistant to therapy

## MICROSCOPIC

### Histologic Features

- Histopathology may overlap with other inactive lymphocytic cicatricial alopecias
- Early CCCA
  - Sparse lymphocytic perifolliculitis of upper hair follicle segment
  - Myxoid concentric/hourglass fibrosis of upper hair follicle segment
  - Loss of sebaceous glands

- Premature desquamation of inner root sheath, often in upper panniculus or lower dermis
- Eccentric atrophy of outer root sheath
- Hair fiber foreign body granulomas
- Late CCCA
  - Atrophic dermis with narrow, horizontally arranged collagen bundles
  - Elastic fibers preserved between atrophic collagen bundles
  - Broad fibrous scars devoid of elastic fibers located at sites of previous follicles

## DIFFERENTIAL DIAGNOSIS

### Follicular Lichen Planus (Lichen Planopilaris)

- Irregular alopecic plaques with more abrupt onset, sometimes multiple
- Patients more likely to be Caucasian and complain of tenderness or itching
- Perifollicular erythema and hyperkeratosis often seen
- Biopsy demonstrates lichenoid inflammation of upper follicle with squamatization, hypergranulosis, superficial wedge-shaped scars devoid of elastic fibers, and numerous IgM(+) perifollicular cytotoid bodies

### Lupus Erythematosus

- Disciform alopecic plaques of atrophic, indurated skin exhibiting carpet tack scale, central hypopigmentation, and peripheral hyperpigmentation
- Biopsy demonstrates epidermal atrophy, vacuolar interface dermatitis, scale, follicular plugging, superficial and deep perivascular dermatitis, inflammation of secretory component of sweat gland, loss of dermal elastic fibers, and increase in colloidal iron (+) dermal mucin
- Direct immunofluorescence may demonstrate lupus band or in vivo ANA

### Androgenetic (Pattern) Alopecia

- Symmetric hair thinning across vertex with preserved frontal hair line in women
- May be difficult to distinguish from early CCCA by physical examination
- Biopsy demonstrates miniaturized vellus-like follicles of various sizes, but hair follicles and sebaceous glands are preserved

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Histopathology may overlap with other forms of cicatricial alopecia, and specific diagnosis often requires knowledge of clinical context
- Premature desquamation of inner root sheath is not unique to CCCA and may be seen in other scarring alopecias
- If only single biopsy is provided, vertical sections are preferred to horizontal sections to better demonstrate elastic fiber pattern
- CCCA may be commingled with androgenetic (pattern) alopecia

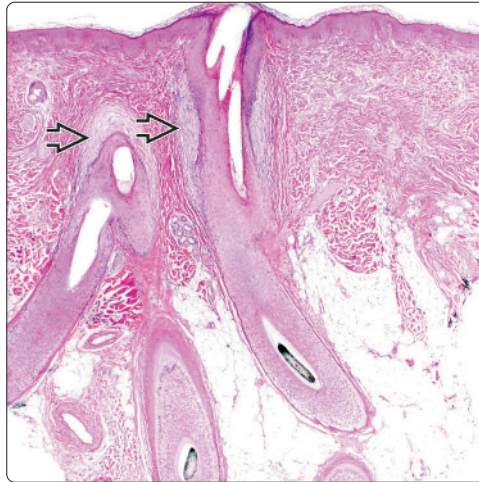
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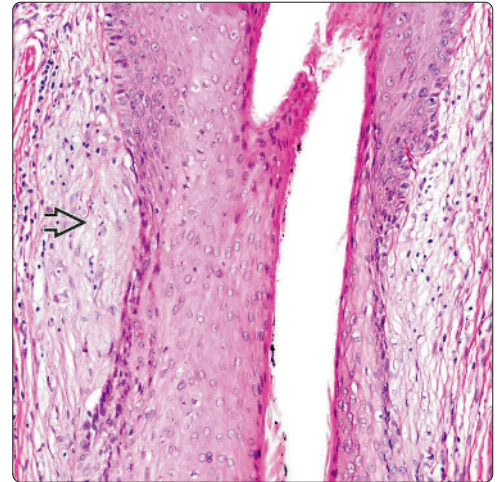
## Central Centrifugal Cicatricial Alopecia

**(Left)** A vertical section demonstrates "hourglass" desmoplasia around the upper segment of the hair follicle. Although hourglass desmoplasia is common to early CCCA, it is not pathognomonic and may be seen in other lymphocytic cicatricial alopecias. Destruction of the hair follicle stem cells in this area produces permanent alopecia. **(Right)** The fibrosis is relatively cell poor and associated with eccentric thinning of the isthmus of the hair follicle.

Hourglass Desmoplasia in Early CCCA

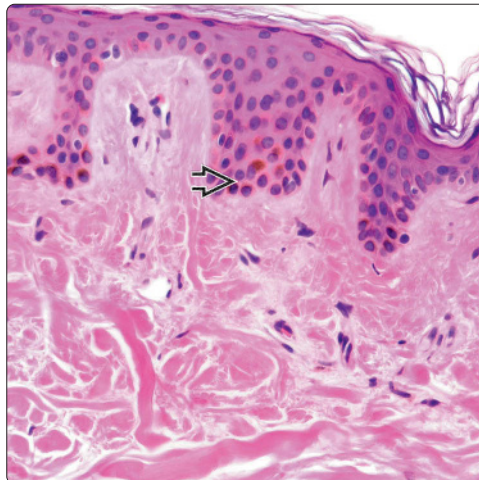


Fibrosis With Eccentric Thinning of Isthmus

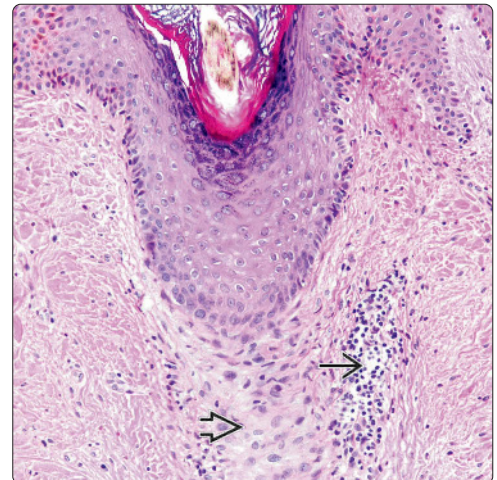


**(Left)** The epidermis is heavily pigmented (a clue to African American skin). Note the absence of interface dermatitis, militating against lupus erythematosus and lichen planus. **(Right)** Sometimes the histopathologic changes in early CCCA are quite subtle. In this section, there is just a hint of perifollicular desmoplasia. Inflammation is sparse in CCCA. Biopsies of active lupus erythematosus and follicular lichen planus exhibit more striking lymphocytic inflammation.

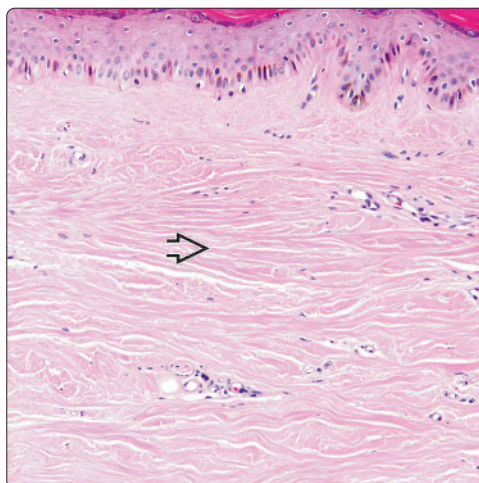
Lack of Interface Changes



Early CCCA With Perifollicular Desmoplasia

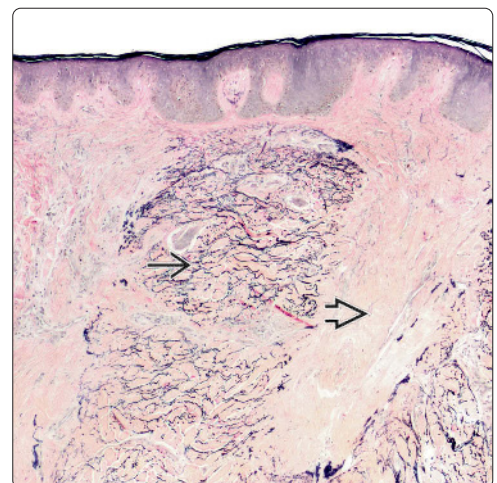


Advanced CCCA With Atrophy and Absence of Hair Follicles



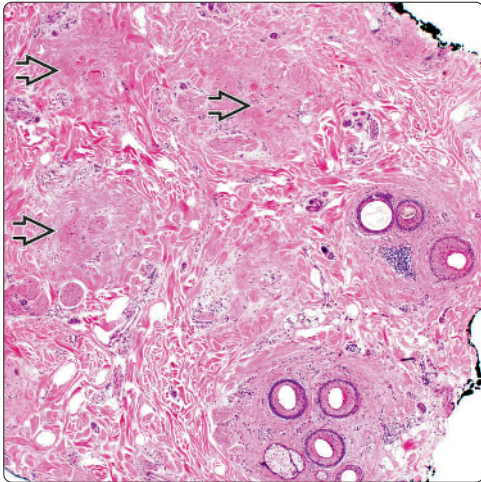
**(Left)** Advanced CCCA produces an atrophic dermis devoid of hair follicles and populated by narrow, closely spaced collagen bundles. **(Right)** Broad fibrous scars correspond to defunct hair follicles in advanced CCCA. The intervening dermis has a preserved elastic fiber network. Follicular lichen planus produces wedge-shaped scars. Lupus erythematosus and neutrophilic cicatricial alopecias produce pan-dermal scarring with diffuse elastic fiber loss.

Broad Scars Demonstrated With Elastic Verhoeff-van Gieson Stain

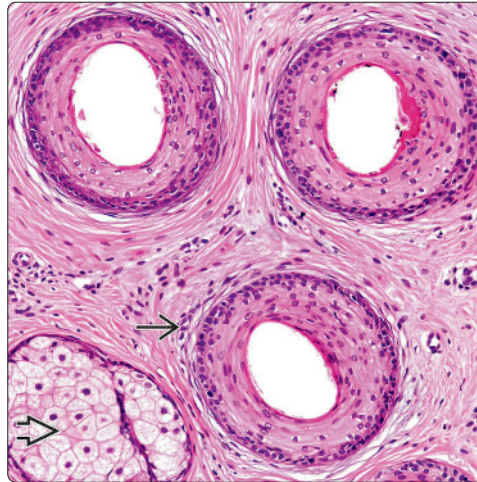




**Decrease in Hair Units With Scarring**

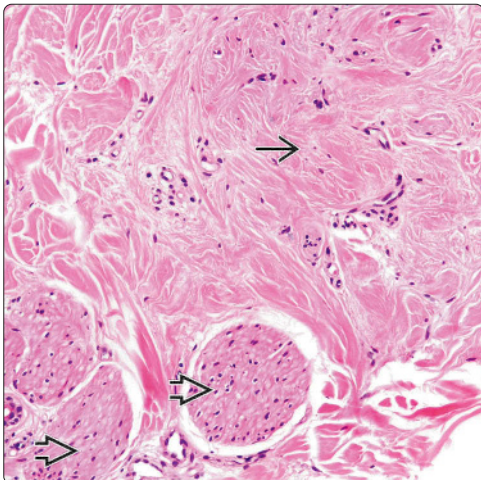


**Concentric Desmoplasia With Loss of Sebaceous Glands**

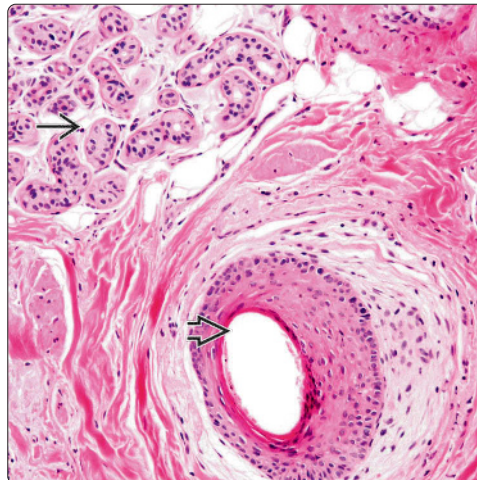


(Left) Horizontal sections can be more sensitive in assessing the extent of hair loss. Hair follicles are normally organized into units composed of a cluster of 2-4 follicles. Some units (3-5 follicles) in this section have been completely replaced by scars. (Right) Sebaceous glands are also destroyed in CCCA. Only a single atrophic sebaceous gland remains in this follicular unit consisting of 3 terminal follicles exhibiting early concentric desmoplasia.

**Remaining Arrector Pili Muscles Adjacent to Scar**

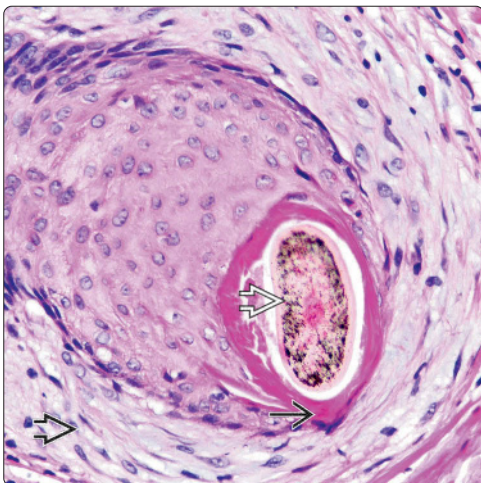


**Premature Desquamation of Inner Root Sheath**

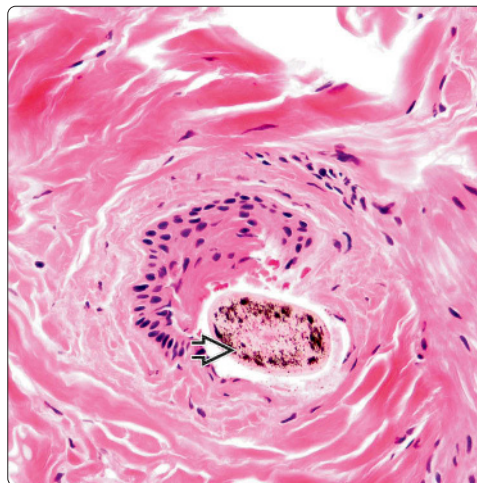


(Left) Lonely arrector pili muscles tend to persist at the site of previous follicular units and can be a clue to subtle follicular scars. (Right) This follicle lacks an inner root sheath, despite being deeply located in the dermis adjacent to an eccrine unit. Premature desquamation is held by some to be prototypic of CCCA, particularly when demonstrated in nonlesional skin. However, it can be seen in a variety of scarring alopecias.

**Concentric Desmoplasia With Eccentric Thinning of Follicle**



**Naked Hair Shaft Being Formed**



(Left) Concentric desmoplasia is accompanied by eccentric thinning of the follicle, creating the opportunity for the hair fiber to perforate through the wall of the follicle. The hair fibers in African Americans are elliptical and can be a clue to the patient's ethnicity. (Right) This hair fiber has just liberated itself from the follicular canal and, if not interrupted by biopsy, would have resulted in a hair fiber granuloma.



## KEY FACTS

## TERMINOLOGY

- Neutrophil-mediated scarring alopecia with follicular pustules

## CLINICAL ISSUES

- Single or multiple plaques of alopecia with painful follicular pustules, crusts, and papules at advancing border
- Predilection for vertex, but may involve any part of scalp; rarely involves other hair-bearing skin
- Doll's hair tufted folliculitis (multiple hairs emerging from single follicle) may be seen, especially if occiput is involved
- Fungal and bacterial cultures are indicated to exclude infectious folliculitis and determine antibiotic sensitivity

## MICROSCOPIC

- Dilation of upper segment of hair follicle with intrafollicular and perifollicular collections of neutrophils
- Extensive scarring with loss of dermal elastic fiber network

- Formation of compound follicles containing multiple hair fibers
- Interstitial lymphoplasmacytic inflammation

## TOP DIFFERENTIAL DIAGNOSES

- Dissecting folliculitis/cellulitis
- Infectious folliculitis
- Follicular lichen planus (lichen planopilaris)
- Brocq pseudopelade
- Central centrifugal cicatricial alopecia

## DIAGNOSTIC CHECKLIST

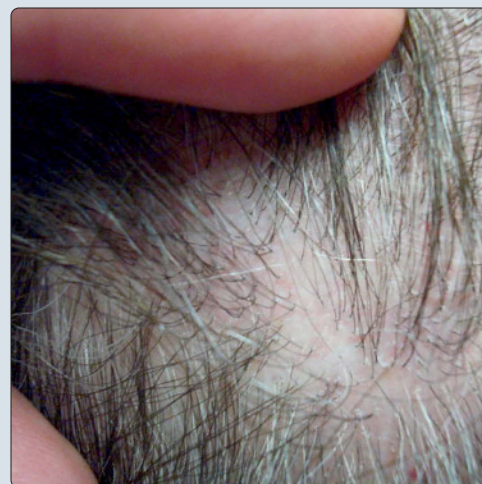
- In advanced folliculitis decalvans, neutrophilic inflammation may be absent
- Compound follicles and pandermal scarring with loss of interstitial elastic fiber network are clues to diagnosis of late-stage folliculitis decalvans

Doll's Hair Follicles

(Left) Late-stage folliculitis decalvans demonstrates an irregular patch of alopecia with rare doll's hair follicles containing multiple hair fibers. (Right) Erythema of the scalp with white areas of scarring hair loss is indicated by "doll's head" appearance. Perifollicular casts at base of hair indicate disease still active in hair follicle.

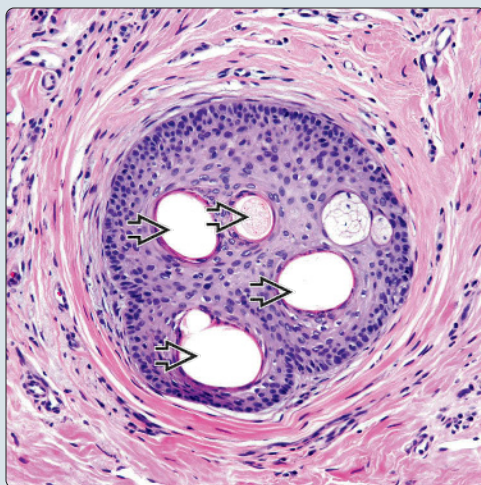


Erythema With Scarring

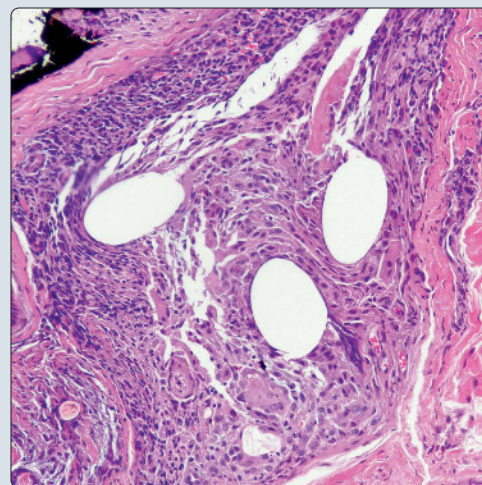


Doll's Hair Follicle Microscopic

(Left) Doll's hair is a result of a compound follicle formed by the fusion of multiple simple follicles. Compound follicles with 4 or more hairs are often seen in folliculitis decalvans. (Right) Advanced folliculitis decalvans demonstrates dermal hair fiber granulomas (the hair fibers have fallen out of the plane of section) with surrounding giant cells. The three empty hair shafts indicate a compound follicle.



Hair Fiber Granulomas





**TERMINOLOGY****Abbreviations**

- Folliculitis decalvans (FD)

**Synonyms**

- Quinquaud disease, tufted folliculitis

**Definitions**

- Neutrophil-mediated scarring alopecia with follicular pustules

**ETIOLOGY/PATHOGENESIS****Infectious Agents**

- *Staphylococcus aureus* can almost always be cultured from pustules, but its role in this disease is unclear

**Genetic**

- In predisposed individuals, bacterial superantigens may evade immune system and induce persistent localized inflammatory reaction that eventually destroys hair follicle stem cells

**CLINICAL ISSUES****Epidemiology**

- Incidence
  - Accounts for 10% of all cicatricial alopecias
- Age
  - Young to middle-aged adults
- Sex
  - Male predominance, though both sexes affected

**Presentation**

- Single or multiple plaques of alopecia with painful follicular pustules, crusts, and papules at advancing border
- Predilection for vertex, but may involve any part of scalp; rarely involves other hair-bearing skin
- Doll's hair tufted folliculitis (multiple hairs emerging from single follicle) may be seen, especially if occiput is involved

**Laboratory Tests**

- Fungal and bacterial cultures are indicated to exclude infectious folliculitis and determine antibiotic sensitivity

**Treatment**

- Drugs
  - Oral antibiotics (clindamycin, rifampin, fusidic acid)
  - Oral zinc supplementation
  - Intralesional corticosteroids to quell inflammation

**Prognosis**

- Variable response to therapy, with some cases progressing to patches of end-stage alopecia

**MICROSCOPIC****Histologic Features**

- Early-stage disease
  - Dilation of upper segment of hair follicle with intrafollicular and perifollicular collections of neutrophils
  - *Staphylococcus aureus* can often be highlighted within inflamed follicles with tissue Gram stain

- Crusts with neutrophils atop inflamed hair follicles
- Premature desquamation of inner root sheath
- Advanced disease
  - Extensive scarring with loss of dermal elastic fiber network
  - Formation of compound follicles containing multiple hair fibers
  - Dermal hair fiber granulomas and perifollicular concentric myxoid fibrosis
  - Interstitial lymphoplasmacytic inflammation

**DIFFERENTIAL DIAGNOSIS****Dissecting Folliculitis/Cellulitis**

- Most patients (80%) are young men of African descent with cutaneous scalp abscesses and draining sinus tracts
- FD predominantly affects Caucasians and does not produce boggy dermal abscesses or sinus tracts

**Infectious Folliculitis**

- Bacterial folliculitis does not usually produce grouped follicular papules
- Fungal folliculitis (kerion) demonstrates fungal elements within follicular abscess
- Microbial cultures should be considered in all cases of FD to exclude primary infectious folliculitis

**Follicular Lichen Planus (Lichen Planopilaris)**

- Irregular plaques of alopecia with perifollicular erythema and hyperkeratosis at advancing border
- Inflammation is primarily lymphocytic and localized to upper hair follicle segment
- Forms wedge-shaped superficial scars rather than pandermal scars
- Plasma cells and neutrophils are rare in follicular lichen planus but common in FD

**Brocq Pseudopelade**

- Multiple noninflammatory, ivory-white, depressed plaques of alopecia in Caucasians
- Elastic fiber network is preserved between broad follicular scars; in late-stage FD, there is loss of interstitial dermal elastic network and more pronounced inflammation




**Central Centrifugal Cicatricial Alopecia**

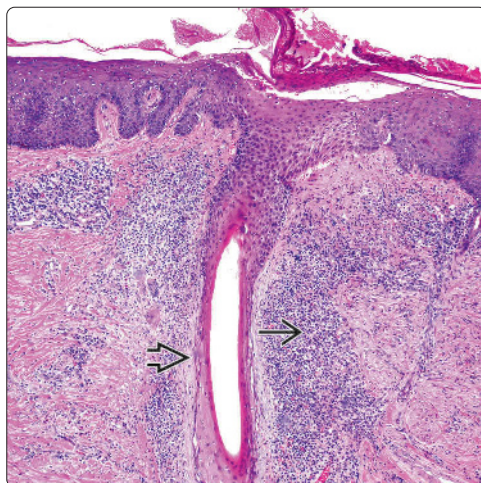
- Single patch of insidiously progressive, asymptomatic, noninflammatory alopecia on vertex of women of African descent
- Histopathology overlaps with late-stage FD (premature desquamation of inner root sheath, concentric perifollicular myxoid fibrosis, and hair fiber granulomas)
- Late-stage FD can be distinguished by identifying compound follicles and pandermal scarring with loss of dermal elastic fiber network

**SELECTED REFERENCES**

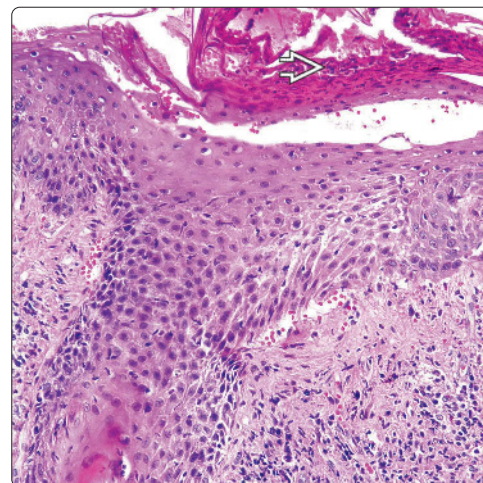
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## Hourglass Thinning of Follicle





(Left) This vertical section demonstrates folliculitis decalvans midway in its evolution. Though classified as a neutrophilic cicatricial alopecia, mononuclear cells  predominate if the biopsy is not centered on a pustule. Hourglass thinning of the follicle  is common but nonspecific. (Right) Small crusts containing degenerated neutrophils  overlying follicles may be a clue to folliculitis decalvans. They represent a devolving pustule.

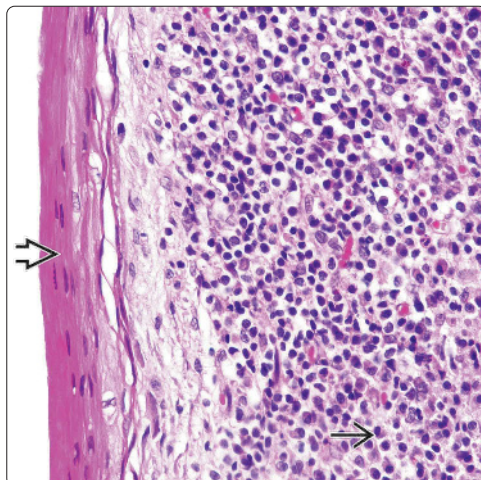


## Crusts With Degenerated Neutrophils

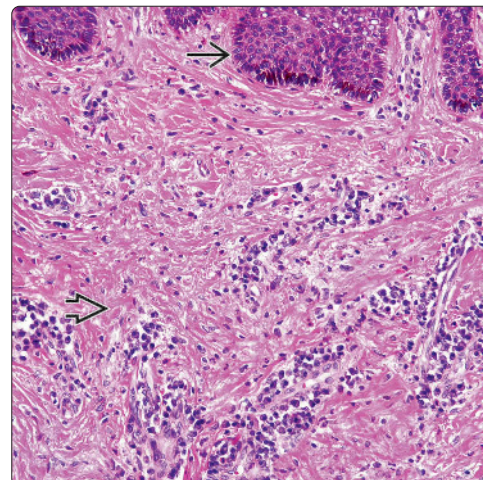


## Mononuclear Infiltrate With Plasma Cells

(Left) The mononuclear infiltrate at the edge of the attenuated follicle  includes copious plasma cells . Plasma cells are seen in fully developed "neutrophilic" cicatricial alopecias but are uncommon in lymphocytic alopecias such as follicular lichen planus. (Right) There is scarring  of the interstitial dermis distant from the follicle. The rete ridge pattern  is preserved, indicating that scarring is due to endogenous dermatitis or folliculitis rather than external trauma.

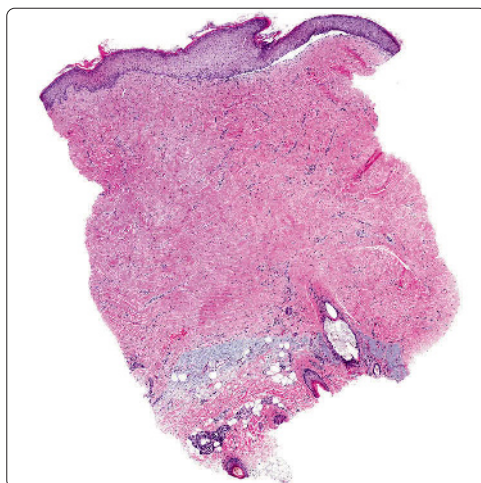


## Dermal Scarring

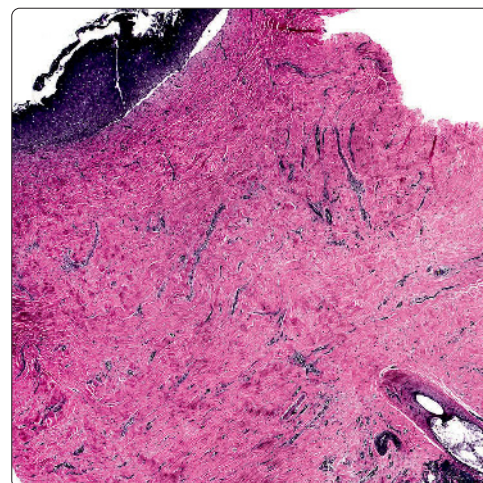


## Pandermal Scarring

(Left) This vertical section of terminal folliculitis decalvans demonstrates pandermal scarring. Scarring to this degree suggests a neutrophil-mediated cicatricial alopecia such as folliculitis decalvans, traumatic injury, or lupus erythematosus. (Right) Elastic fiber stains performed on vertical sections can be very helpful in evaluating late-stage cicatricial alopecias. Pandermal scarring is highlighted by the absence of elastic fibers throughout the dermis.

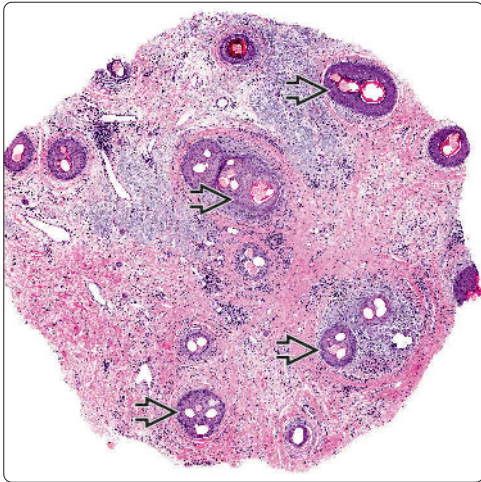


## Absence of Elastic Fibers in Scarring





**Compound Follicles**

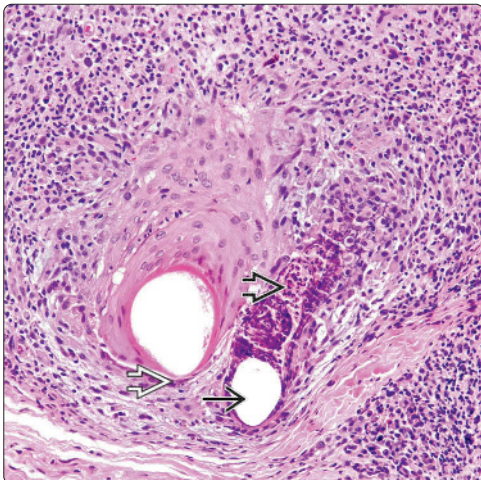


**Compound Follicle With Numerous Hair Fibers**

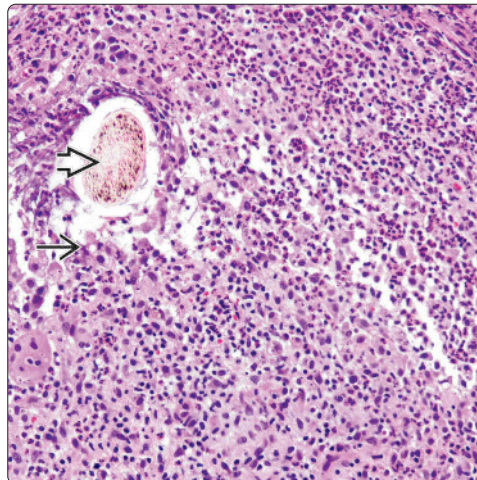


(Left) Horizontal sections can be very useful in identifying compound follicles. Ideally, 2 biopsies should be submitted when evaluating cicatricial alopecia to allow examination of both vertical and horizontal sections. (Right) There are > 6 hair fibers in this compound follicle. "Six-pack" compound follicles provide compelling evidence of a neutrophil-mediated cicatricial alopecia such as folliculitis decalvans.

**Perifollicular Abscess**

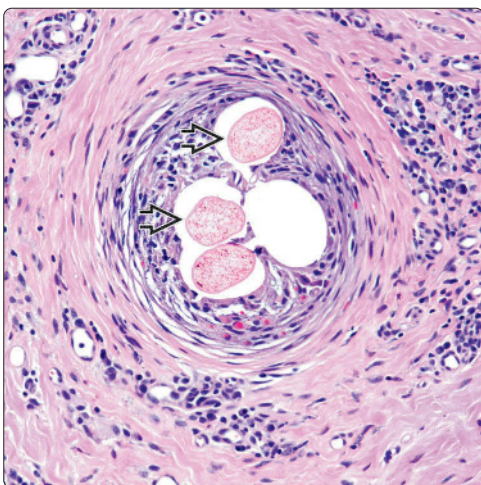


**Granulomatous Reaction to Naked Hair Shaft**

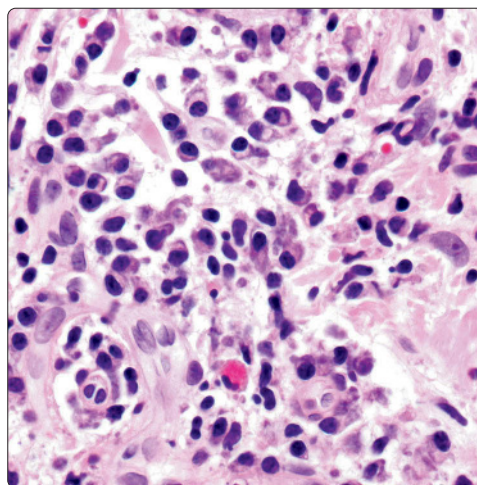


(Left) There is a perifollicular abscess composed of neutrophils and surrounding an empty space corresponding to an extruded hair fiber that separated from the paraffin section during slide staining. The eccentric thinning of the adjacent follicle reflects the point of exit of the hair fiber and can also be seen in central centrifugal cicatricial alopecia. (Right) The extruded hair fiber in this section has stimulated a granulomatous reaction.

**Compound Fiber Foreign Body Granuloma**



**Numerous Plasma Cells**



(Left) Ruptured compound follicles result in compound hair fiber foreign body granulomas. This complex of 4 hair fibers suggests the original compound follicle contained 4 hair fibers, indicating a neutrophil-mediated cicatricial alopecia. (Right) There are aggregates of plasma cells in the scarred interstitial dermis. This is seen in advanced folliculitis decalvans and acne keloidalis nuchae; acne keloidalis nuchae produces keloidal scarring and raised lesions.



## KEY FACTS

### TERMINOLOGY

- Definition: Pruritic, painful, keloid-like papules and plaques with alopecia secondary to inflammation and scarring of hair follicles

### CLINICAL ISSUES

- Mostly in young adults (ages 14-25)
- More common in men
- More common in those of African heritage
- Pruritic or painful follicular papules and pustules
- Over time, individual lesions coalesce into band-like, indurated plaques
- Occipital scalp and neck

### MICROSCOPIC

- Early lesions
  - Acute neutrophilic infiltrate in follicular isthmus, infundibulum, and surrounding sebaceous glands
- Later lesions

- Chronic lymphocytic inflammation of isthmus and infundibulum
- Dermal fibrosis, destruction of the follicular wall, and scattered naked hair shafts
- Granulomatous inflammation and dense plasma cell infiltrate may be seen

### TOP DIFFERENTIAL DIAGNOSES

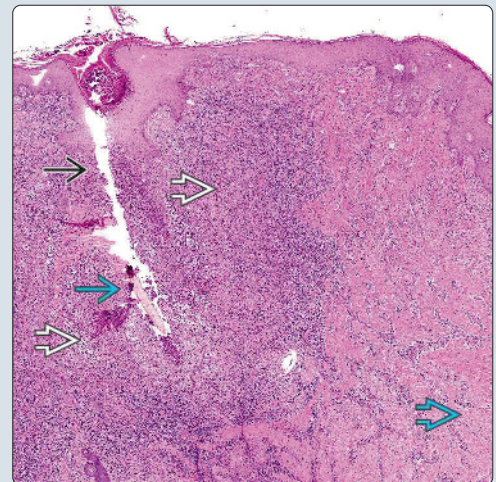
- Folliculitis decalvans
- Central centrifugal scarring alopecia
- Deep infectious folliculitis
- Acne vulgaris
- Acne conglobate
- Hidradenitis suppurativa
- Perifolliculitis capitis abscedens et suffodiens

**Numerous Follicular Papules**

(Left) Nuchal area of scalp in a person of color shows numerous dome-shaped follicular papules as is typical for early lesions of acne keloidalis nuchae. Some are coalescing to form plaques. (Right) Dense, mixed perifollicular inflammation with destruction of follicle, naked hair shafts, and adjacent dermal fibrosis is shown.

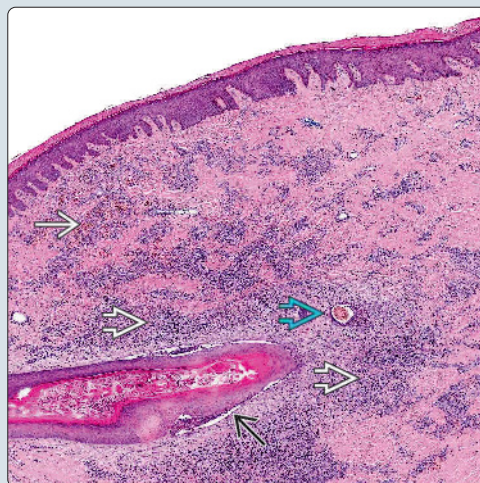


**Naked Hair Shaft With Mixed Perifollicular Inflammation**

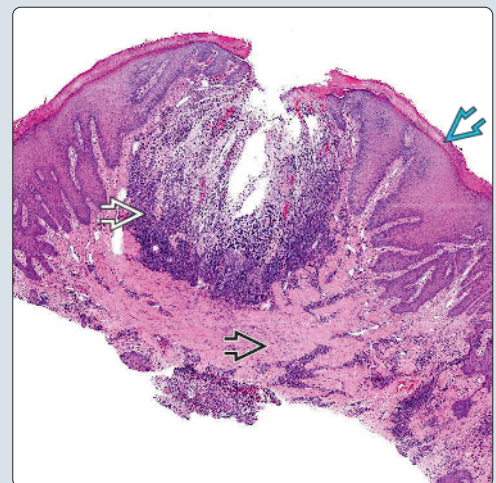


**Perifollicular Inflammation, Hemosiderin Deposition and Naked Hair Shafts**

(Left) Dense dermal and perifollicular inflammation with hemosiderin deposition is shown. Follicle oriented parallel to the epidermal surface shows disruption of follicular epithelium. Naked hair shaft is shown. (Right) Localized dense mixed inflammatory infiltrate with adjacent dermal fibrosis, epidermal acanthosis, and parakeratosis is shown.



**Dense Mixed Infiltrate With Adjacent Dermal Fibrosis**





**TERMINOLOGY****Synonyms**

- Sycosis frambesiformis
- Dermatitis papillaris capillitii
- Folliculitis keloidalis
- Folliculitis nuchae
- Folliculitis keloidalis nuchae
- Acne keloidalis

**Definitions**

- Pruritic, painful, keloid-like papules and plaques with alopecia secondary to inflammation and scarring of hair follicles

**ETIOLOGY/PATHOGENESIS****Possible Connection to Chronic Irritation**

- Rubbing (clothing, athletic gear, helmets)
- Seborrheic dermatitis

**Exacerbating Factors**

- Coarse, curly hair
- Androgen excess
- Cyclosporine, carbamazepine, diphenylhydantoin

**CLINICAL ISSUES****Epidemiology**

- Age
  - Mostly in young adults (ages 14-25)
- Sex
  - More common in men
- Ethnicity
  - More common in those of African heritage

**Presentation**

- Pruritic or painful follicular papules and pustules
  - Over time, individual lesions coalesce into band-like indurated plaques
- Occipital scalp and neck
- Abscesses and sinus tracts may be present
- Leads to scarring alopecia, tufted doll-like hairs

**Prognosis**

- Benign condition
- Can be medically managed with early intervention
- Once severe scarring occurs, plaques can continue to expand and hair loss is permanent
  - Can be painful and aesthetically displeasing to patients

**MACROSCOPIC****General Features**

- Early stage: Dome-shaped, folliculocentric papules (2-4 mm) on occipital scalp
  - Pustules may be present
- Late stage: Scarring alopecia with keloid-like plaques in a band-like distribution
  - Can extend > 10 cm

**MICROSCOPIC****Histologic Features**

- Early lesions
  - Acute neutrophilic infiltrate in follicular isthmus, infundibulum, and surrounding sebaceous glands
- Later lesions
  - Chronic lymphocytic inflammation of isthmus and infundibulum
  - Dermal fibrosis, destruction of follicular wall, and scattered naked hair shafts
  - Granulomatous inflammation and dense plasma cell infiltrate may be seen
  - True keloidal collagen is not seen

**Predominant Pattern/Injury Type**

- Superficial and deep mixed inflammatory infiltrate with dermal scarring and follicular disruption

**ANCILLARY TESTS****Histochemistry**

- Special stains (PAS) to rule out fungal process

**Culture**

- Aerobic/anaerobic bacteria and fungal

**DIFFERENTIAL DIAGNOSIS****Folliculitis Decalvans**

- Less fibrosis, similar neutrophilic infiltrate around isthmus in early lesions

**Central Centrifugal Scarring Alopecia**

- Affects midline scalp in African Americans

**Deep Infectious Folliculitis**

- Will have positive cultures, less follicular disruption, and less dermal scarring

**Acne Vulgaris**

- Also involves the pilosebaceous unit, unlikely to cause alopecia

**Acne Conglobate**

- Can cause keloidal and atrophic scarring on chest, back, extremities, and face

**Hidradenitis Suppurativa**

- Affects intertriginous regions

**Perifolliculitis Capitis Abscedens et Suffodiens**

- Dissecting cellulitis of scalp, common in black males, suppurative nodules with fistulous tracts

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## KEY FACTS

### CLASSIFICATION

- Perifolliculitis capitis abscedens et suffodiens, a.k.a. scarring alopecia

### CLINICAL ISSUES

- Presents on occiput or vertex as fluctuant interconnecting nodules of inflammation that wax and wane over time, primarily affecting vertex and occiput scalp, typically of young African American male patients
- Different stages of inflammation within scalp can be seen at any time, including discharge from active boggy nodules to hypertrophic scars

### MICROSCOPIC

- Early findings
  - Perifollicular and follicular mixed inflammatory infiltrate especially at infundibulum
  - Abscess formation is common, along with sinus tract formation

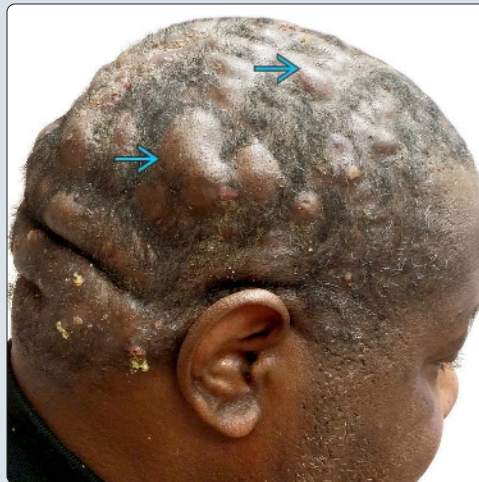
- Free hair shafts in dermis can elicit more acute inflammatory infiltrate (neutrophils, etc.)
- As it progresses, giant cells, macrophages, plasma cells can be seen admixed with lymphocytes and neutrophils
- Late findings
  - Hair follicles and sebaceous glands are obliterated
  - Increased fibrosis and scar formation
  - Increased number of catagen and telogen hairs

### TOP DIFFERENTIAL DIAGNOSES

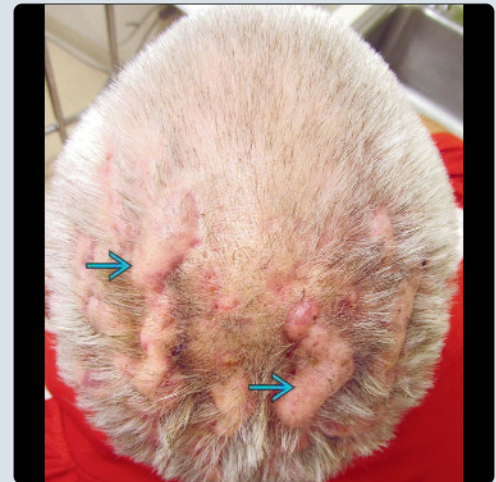
- Folliculitis decalvans
  - Primarily neutrophilic cicatricial alopecia with dilatation of infundibulum, keratin aggregation
  - Prefers vertex, occiput, with perifollicular erythema, as well as tufting of hair follicles
- Pseudopelade of Brocq (might represent end-stage scarring not otherwise specified)
  - Difficult to differentiate from any of scarring alopecias when only scarring and fibrosis are present

#### Fluctuant Interconnecting Nodules

(Left) Clinical photograph shows an African American man with full scalp involvement of fluctuant interconnecting nodules. The nodules display areas of scarring alopecia. (Courtesy E. Lilly, MD.) (Right) Clinical photograph shows a Caucasian man with vertex-occipital scalp involvement of fluctuant interconnecting nodules. The nodules display areas of scarring alopecia. (Courtesy K. Huang, MD.)

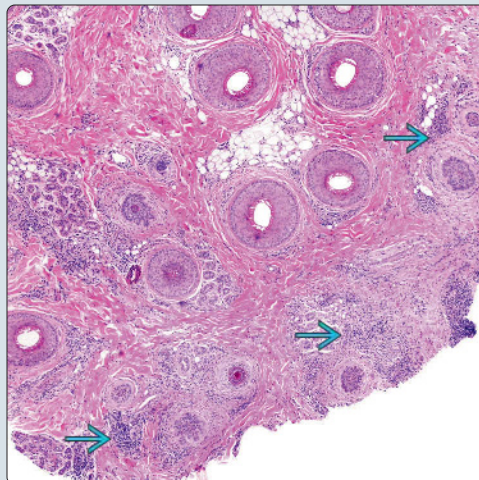


#### Fluctuant Nodules With Areas of Scarring

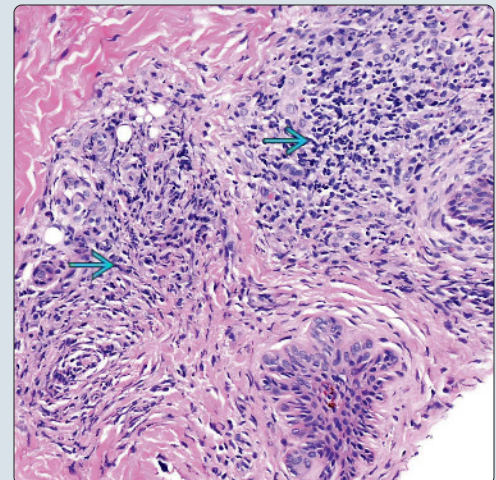


#### Perifollicular Mixed Inflammation

(Left) Medium-power image of a horizontal section demonstrates a perifollicular mixed inflammatory infiltrate at the level of the dermal subcutaneous junction. This would be considered an early lesion. (Right) High-power image of a horizontal section demonstrates a perifollicular mixed inflammatory infiltrate.



#### Perifollicular Mixed Infiltrate, High Power





**TERMINOLOGY****Synonyms**

- Perifolliculitis capitis abscedens et suffodiens
- Perifolliculitis capitis
- Scalp folliculitis
- Folliculitis abscedens et suffodiens

**Definitions**

- Scarring alopecia that preferentially affects young African American men, but can affect anyone
- Part of "follicular occlusion triad," which includes acne conglobata and hidradenitis suppurativa
  - Sometimes referred to as "tetrad" when pilonidal sinus occurs

**CLINICAL ISSUES****Presentation**

- Presents on occiput or vertex as fluctuant interconnecting nodules of inflammation that wax and wane over time
  - Primarily affects vertex and occiput scalp
- Typically affects young African American men, but anyone can be affected
- Different stages of inflammation within scalp can be seen at any time
  - May include discharge from active boggy nodules to hypertrophic scars
- Discharge can be foul smelling at times

**Treatment**

- Options, risks, complications
  - Systemic antibiotics, intralesional steroids, tumor necrosis factor- $\alpha$  inhibitors, or isotretinoin can be considered, although there is no curative guarantee

**Prognosis**

- Scarring with alopecia is expected

**MICROSCOPIC****Histologic Features**

- Early findings
  - Perifollicular and follicular mixed inflammatory infiltrate, especially at infundibulum
  - Free hair shafts in dermis can elicit more acute inflammatory infiltrate (neutrophils, etc.)
  - As it progresses, giant cells, macrophages, plasma cells can be seen admixed with lymphocytes and neutrophils
  - Abscess formation is common, along with sinus tract formation
- Late findings
  - Hair follicles and sebaceous glands are obliterated
  - Increased fibrosis and scar formation
  - Increased number of catagen and telogen hairs

**DIFFERENTIAL DIAGNOSIS****Histopathologic**

- Folliculitis decalvans
  - Primarily neutrophilic cicatricial alopecia with dilatation of infundibulum, keratin aggregation
- Pseudopelade of Brocq

- Might represent end-stage scarring not otherwise specified
- Difficult to differentiate from any of scarring alopecias when only scarring and fibrosis are present
  - Fibrotic streamers in place where follicles once existed

**Clinical**

- Folliculitis decalvans
  - Prefers vertex, occiput, with perifollicular erythema, as well as tufting of hair follicles
- Acne keloidalis nuchae
  - Preferentially affects occiput of dark-skinned individuals
  - End stage is with scars (not true keloids)
- Pseudopelade of Brocq
  - Might represent end-stage scarring not otherwise specified
  - Small patch of hair loss where single hairs persist
    - Female patients affected more

**DIAGNOSTIC CHECKLIST****Clinically Relevant Pathologic Features**

- Presents on occiput or vertex as fluctuant interconnecting nodules of inflammation that wax and wane over time
  - Primarily affects vertex and occiput scalp
  - Typically of young African American male patients

**Pathologic Interpretation Pearls**

- Perifollicular and follicular mixed inflammatory infiltrate, especially at infundibulum
- Abscess and sinus tract formation common in early lesions

**SELECTED REFERENCES**

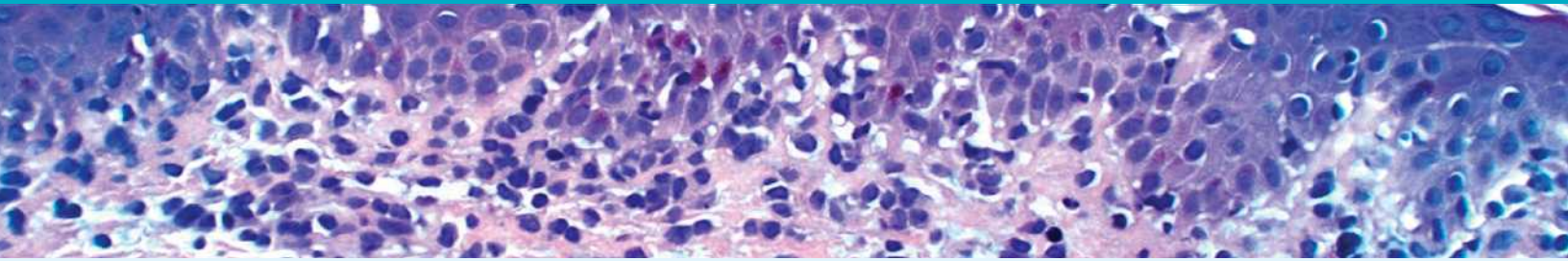
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## SECTION 13

# Reactions to Drugs



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# Morbilloform Drug Reactions

## KEY FACTS

### TERMINOLOGY

- Maculopapular rash resembling measles with temporal relationship to consumption of new drug

### CLINICAL ISSUES

- Most common form of drug reaction estimated to account for 40-90% of all cutaneous drug reactions depending on study
- Erythematous macules and papules appearing 1st on trunk or in areas of pressure/trauma with subsequent symmetrical peripheral spread

### MICROSCOPIC

- Histologic findings are often nonspecific
  - Clinical correlation is important to rule out differential diagnoses
- Superficial perivascular and interstitial dermal infiltrate
  - Most often polymorphous infiltrate of lymphocytes, neutrophils, and eosinophils

- Eosinophils not present in all cases
- Vacuolar interface change
- Scattered necrotic keratinocytes along dermal-epidermal junction

### TOP DIFFERENTIAL DIAGNOSES

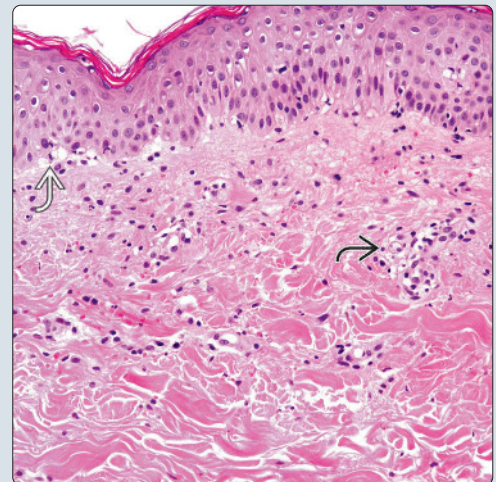
- Early graft-vs.-host disease
- Erythema multiforme
- Connective tissue disease
- Viral exanthem
- Urticaria
- Leukocytoclastic vasculitis

**Pink, Symmetric Maculopapules**

(Left) Classic morbilliform drug eruption developed in this patient after trimethoprim-sulfamethoxazole therapy. Pink, symmetric maculopapules over the anterior thighs are characteristic. (Right) Histologically, morbilliform drug reactions (MDRs) often show a superficial perivascular [1] and interstitial infiltrate [2] with vacuolar change [3].

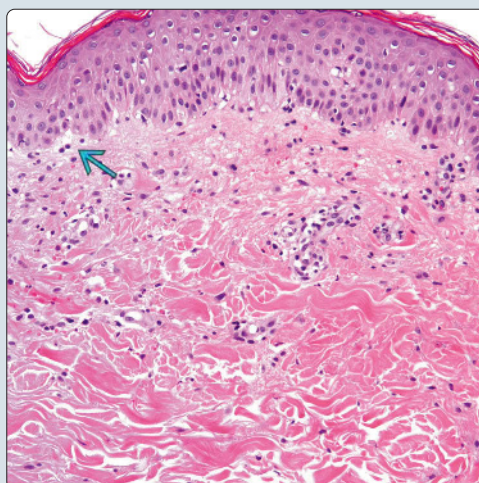


**Perivascular and Interstitial Infiltrate**

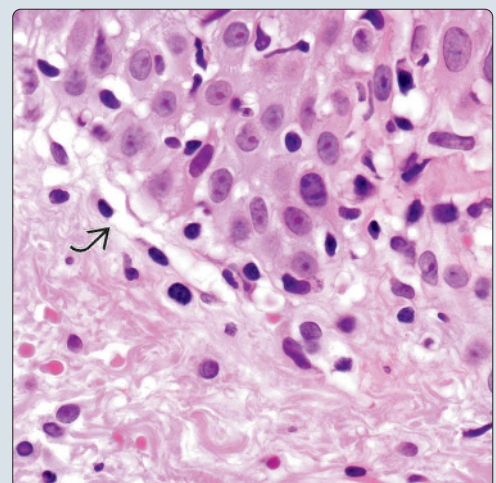


**Superficial and Interstitial Infiltrate**

(Left) This image of a morbilliform drug eruption demonstrates a superficial perivascular and interstitial infiltrate. Some focal interface changes [4] can also be appreciated. (Right) Higher power view demonstrates basal cell vacuolar change [5] and interface dermatitis composed of mainly lymphocytes.



**Vacuolar Change**





## TERMINOLOGY

### Abbreviations

- Morbilloform drug reaction (MDR)

### Synonyms

- Morbilloform exanthem
- Exanthematous drug reaction
- Maculopapular drug eruption/exanthem

### Definitions

- Maculopapular rash resembling measles (morbilloform) that has temporal relationship to consumption of new drug

## ETIOLOGY/PATHOGENESIS

### Drug Exposure

- Immunologic response to drug leads to upregulation of CD54 in keratinocytes and increased levels of IL-5, IL-6, TNF- $\alpha$ , and IFN- $\gamma$ 
  - Cytotoxic CD4(+) and CD8(+) T lymphocytes (CD4 > CD8) that secrete granzyme-B and perforin cause tissue injury
- Antimicrobial drugs [penicillins (especially ampicillin), cephalosporins, sulfonamides, gentamicin, amphotericin B] by far most often implicated
- Barbiturates, NSAIDs, and numerous others also commonly implicated

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Most common form of drug reaction, estimated to account for 40-90% of all cutaneous drug reactions depending on study
  - Incidence increases with
    - Advancing age, concomitant viral infection (HIV, mononucleosis, CMV, human herpesvirus 6), immunosuppression, and total number of drugs
- Age
  - More common in older patients
- Sex
  - M < F

### Presentation

- Blanchable erythematous macules and papules appearing 1st on trunk or in areas of pressure/trauma with subsequent symmetrical peripheral spread
  - Pustules, bullae, or vesicles may also rarely be seen
- Typically arises within 1 week of initiation of drug

### Prognosis

- Excellent
  - Rash resolves rapidly after discontinuation of drug

## MICROSCOPIC

### Histologic Features

- Histologic findings are often nonspecific, but article by Gerson et al provides good summary
- Most common features
  - Superficial perivascular and interstitial dermal infiltrate

- Infiltrate may occasionally extend to mid (~ 15% of cases) or deep dermis (~ 5% of cases)
- Infiltrate can be composed of
  - Lymphocytes only (~ 1/3 of cases)
  - Lymphocytes and eosinophils (~ 1/3 of cases)
  - Lymphocytes, neutrophils, and eosinophils (~ 20% of cases)
  - Lymphocytes and neutrophils (~ 10% of cases)
  - Neutrophils only (~ 5% of cases)
- Vacuolar interface changes are found in ~ 1/2 of all cases
- Other common features
  - Focal mild spongiosis of lower epidermis
  - Scattered necrotic keratinocytes at dermal-epidermal junction
  - Mild superficial papillary dermal edema and vascular dilatation

## DIFFERENTIAL DIAGNOSIS

### Early Graft-vs.-Host Disease

- Clinically indistinguishable, although early graft-vs.-host disease is more confluent and more apt to involve palms/soles and mucous membranes
- Necrotic keratinocytes at all levels of epidermis with "satellite cell necrosis"
- Interface changes typically also involve hair follicles and eccrine glands

### Erythema Multiforme

- Clinically, palm/sole involvement more common and characteristic targetoid/"bull's-eye" lesions
- Histologically, typically has more necrotic keratinocytes, sometimes with vesicle formation, and eosinophils are rare to absent

### Connective Tissue Disease

- Clinically, positive serologies (ANA, others), joint or muscle pain
- Histologically, epidermal atrophy, focal parakeratosis (can be seen in late lesions of MDR), and dermal mucin

### Viral Exanthem

- Clinically, usually fever and malaise
- Histologically, hemorrhage and typically no eosinophils

### Urticaria

- Clinically, evanescent (disappears or changes location in 12-24 hour period or less)
- Histologically, no vacuolar/interface change or necrotic keratinocytes

### Leukocytoclastic Vasculitis

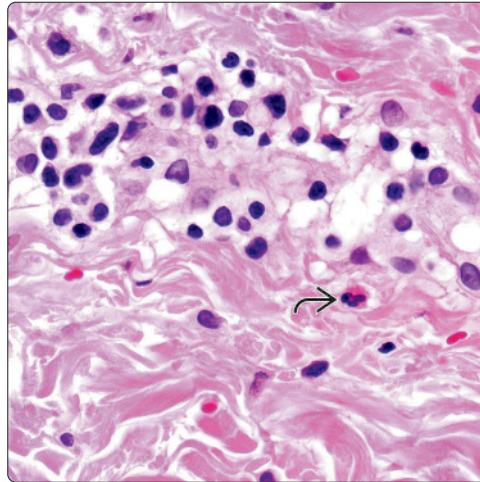
- Clinically, variations of color in same lesion,  $\pm$  necrotic centers
- Histologically, vessel damage present by definition

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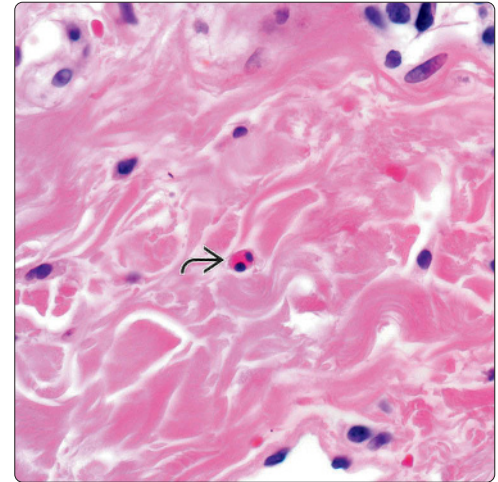
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2. Ramdial PK et al: Drug-induced cutaneous pathology. *J Clin Pathol.* 62(6):493-504, 2009

(Left) Perivascular and interstitial lymphocytes are found in the majority of lesions. Neutrophils and eosinophils are also very commonly seen. (Right) Eosinophils, although a clue to the diagnosis of a drug eruption, are not always seen (in one large study, they were present in only ~ 1/2 of cases).

Neutrophil



Eosinophil

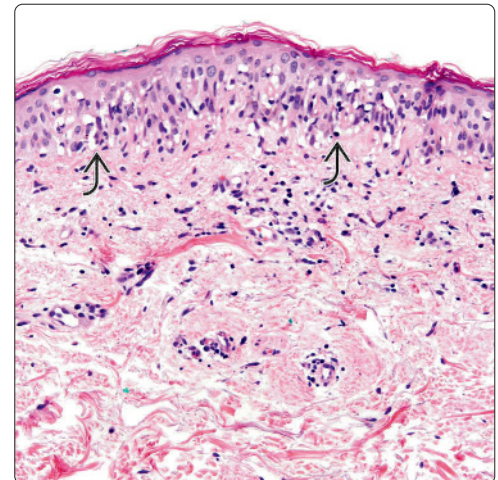


Morbilliform Eruption Secondary to Zolpidem

(Left) This is a morbilliform drug eruption due to zolpidem in an elderly man that began on the trunk and spread peripherally. The eruption rapidly cleared after discontinuation of the medication. (Right) Another case of MDR demonstrates a spongiotic, vacuolar basal cell change with a superficial perivascular and interstitial infiltrate composed of lymphocytes and neutrophils.

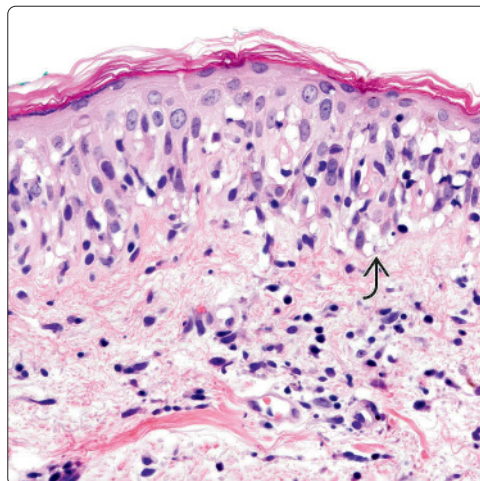


Spongiosis and Vacuolar Change

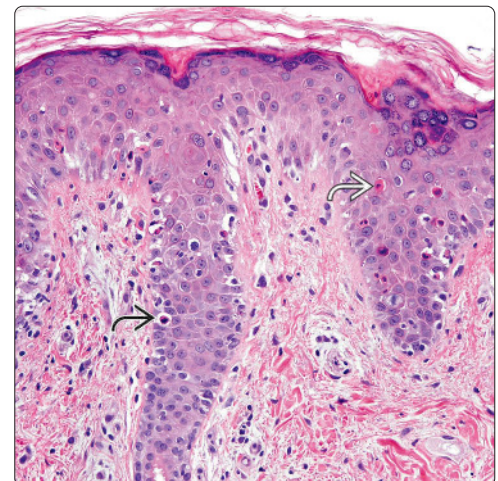


Robust Vacuolar Change

(Left) A higher power view of MDR shows more robust vacuolar change. There is also slight spongiosis. Necrotic keratinocytes are not always seen. (Right) This case of acute graft-vs.-host disease demonstrates numerous necrotic keratinocytes at all levels of the epidermis. There is also involvement of the acrosyringium.

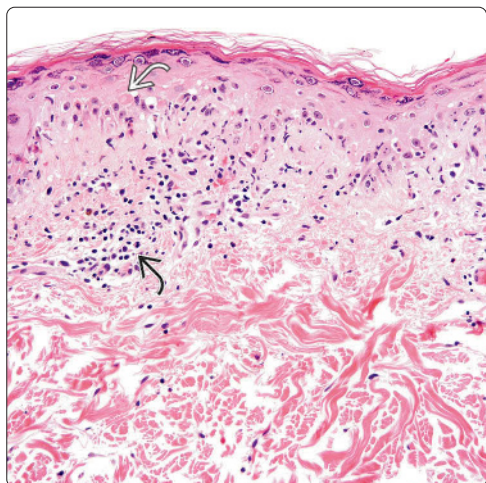


Necrotic Keratinocytes in Early Graft-vs.-Host Disease

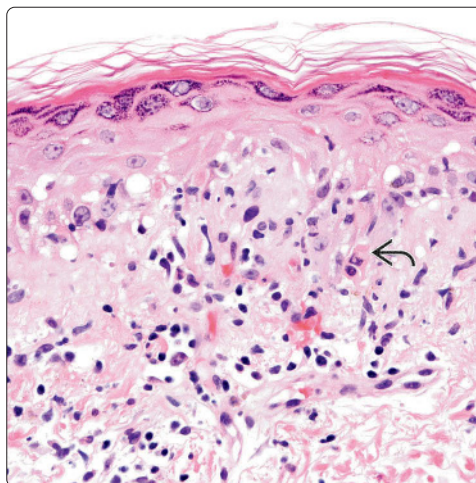




**Necrotic Keratinocytes in Erythema Multiforme**

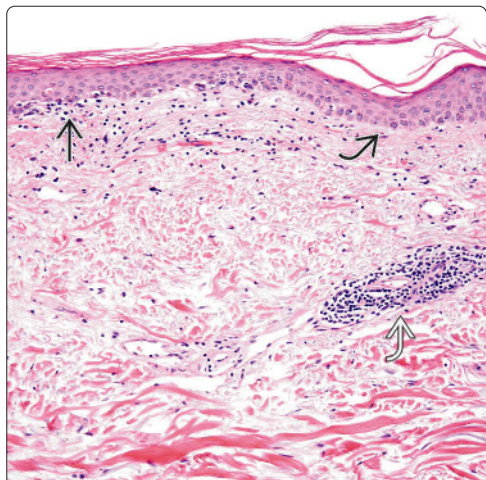


**Interface Changes in Erythema Multiforme**

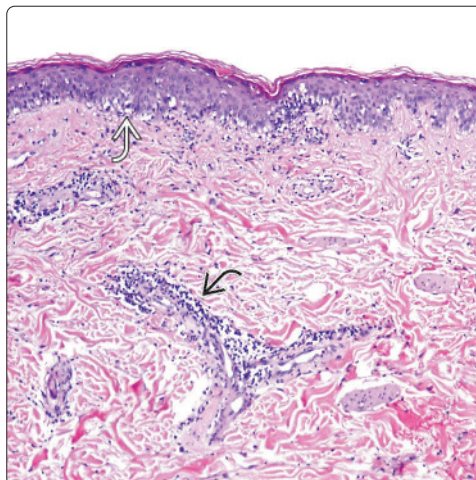


(Left) Erythema multiforme can also demonstrate a superficial perivascular and interstitial inflammatory infiltrate with interface changes. Conspicuous necrotic keratinocytes in the lower epidermis can also be seen. (Right) Higher power view of a case of erythema multiforme demonstrates conspicuous necrotic keratinocytes and more robust interface changes than would typically be expected for MDR. Eosinophils are typically absent.

**Interface Changes in Dermatomyositis**

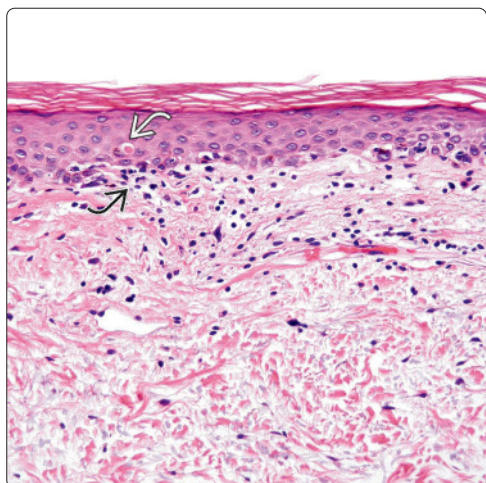


**Vacuolar Interface Change in Lupus Profundus**

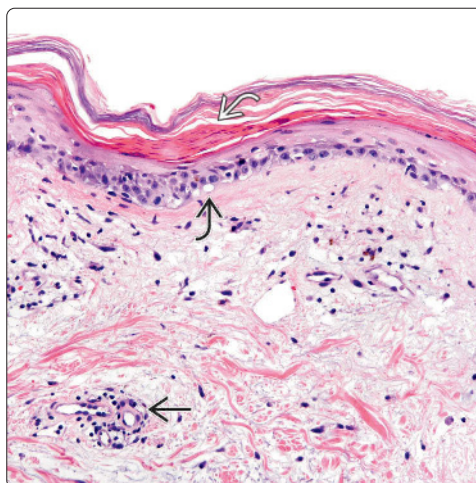


(Left) This biopsy of dermatomyositis demonstrates epidermal atrophy, a superficial mononuclear perivascular infiltrate, and some interface changes. (Right) This case of lupus profundus superficially demonstrates similar vacuolar interface changes. The perivascular infiltrate, however, extends quite deep and diffusely involved the subcutis in this biopsy (not shown).

**Epidermal Atrophy in Dermatomyositis**



**Basal Vacuolar Change in Subacute Cutaneous Lupus**



(Left) Higher power view of a biopsy of dermatomyositis shows epidermal atrophy, interface change, dermal mucin deposition, and a rare necrotic keratinocyte (colloid body). (Right) A biopsy of subacute cutaneous lupus erythematosus (SCLE) can show similar basal layer vacuolization, interface changes, and a superficial perivascular infiltrate. However, epidermal atrophy, interstitial mucin, focal parakeratosis, and clinical history would favor SCLE.



## Fixed Drug Eruption

## KEY FACTS

## TERMINOLOGY

- Recurrent oval, hyperpigmented lesions with halo of erythema occurring at same mucosal or cutaneous sites following exposure to causative drug

## CLINICAL ISSUES

- Initial solitary lesion typically on lips, genitalia, proximal extremity, hip, or lower back as oval erythematous patch, often with burning  $\pm$  itching
- Subsequent episodes occur at same site as well-defined oval hyperpigmented patch surrounded by rim of erythema

## MICROSCOPIC





- Initial episode
  - Normal "basketweave" stratum corneum
  - Interface dermatitis with necrotic keratinocytes
  - Neutrophils &/or eosinophils in addition to lymphocytes
- Subsequent episodes
  - Identical findings from initial episode plus

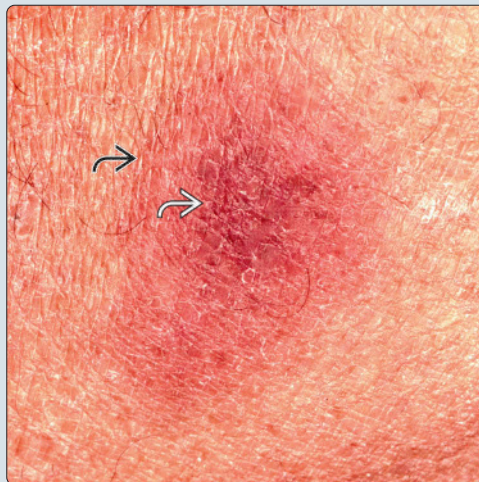
- Papillary dermal fibrosis
- Pigment incontinence with melanophages around postcapillary venules

## TOP DIFFERENTIAL DIAGNOSES

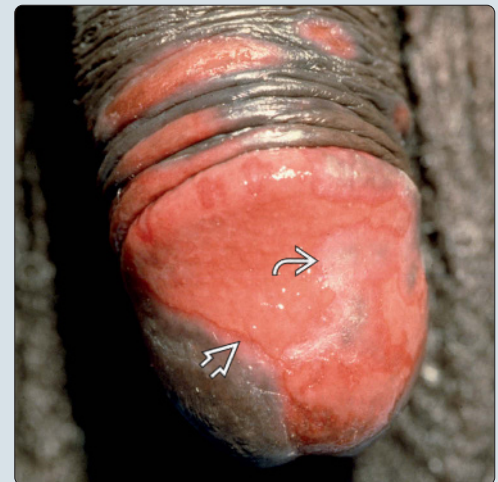
- Urticarial pemphigoid
  - Lacks papillary dermal fibrosis and melanophages around postcapillary venules
- Erythema annulare centrifugum
  - Superficial perivascular lymphoid infiltrate, focal spongiosis, and trailing parakeratotic scale
- Erythema dyschromicum perstans
  - Atrophic lichenoid interface dermatitis with pigment incontinence
- Erythema multiforme
  - Lymphocytes only, with no eosinophils or neutrophils
- Acute urticarial reaction
  - Neutrophils in lumina of postcapillary venules
  - No interface change

Recurrent Fixed Drug Eruption With Outer Rim of Erythema





(Left) Recurrent fixed drug eruption (FDE) presents as an oval erythematous patch with characteristic central area of hyperpigmentation  and outer rim of erythema  on the same cutaneous site after reexposure to the causative drug. (Right) FDE of the glans penis (mucosal site) commonly results in bullae  and erosions .

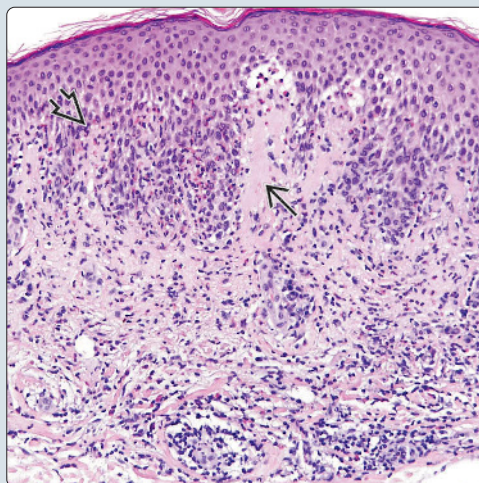


Erosions and Bullae on Glans Penis

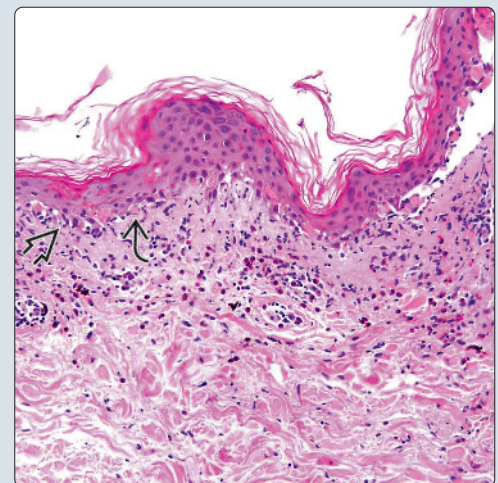


Basket-Weave Stratum Corneum With Interface Changes

(Left) FDE is characterized by a normal basketweave stratum corneum, interface dermatitis  with keratinocyte necrosis, and papillary dermal fibrosis . (Right) Normal basketweave stratum corneum, interface dermatitis  with keratinocyte necrosis , pigment around postcapillary venules, and papillary dermal fibrosis are typical findings in FDE.



Interface Dermatitis With Necrotic Keratinocytes





## TERMINOLOGY

### Abbreviations

- Fixed drug eruption (FDE)

### Definitions

- Recurrent oval, hyperpigmented lesions with halo of erythema occurring at same mucosal or cutaneous sites following exposure to causative drug

## ETIOLOGY/PATHOGENESIS

### Type IV Hypersensitivity Reaction

- During quiescent phase, memory CD8(+) cells, which are protected from apoptosis by keratinocyte-produced IL-15, provide population of memory cells that allow for subsequent reactions
- With each exposure, drug acts as hapten, binding to basal keratinocytes
- CD8(+) memory cells already in place, liberating IFN- $\gamma$  and TNF- $\alpha$  but little IL-2 and IL-4
- During downregulatory phase, CD4(+), CD25(+) T cells capable of producing IL-10 migrate into lesional epidermis
  - Downregulating T cells remove most of expanded clone by apoptosis, but population of CD8(+) memory cells remains to reinitiate process with next exposure

### Implicated Drugs

- Antibacterial agents
  - Trimethoprim-sulfamethoxazole (single most common agent),  $\beta$ -lactams, fluoroquinolones, tetracyclines, erythromycin, clarithromycin, and rifampicin
- Antifungal agents
  - Azoles, griseofulvin, and terbinafine
- Psychoactive agents
  - Barbiturates, opium alkaloids, chloral hydrate, ondansetron, anticonvulsants, chlordiazepoxide, chloral hydrate, and carbamazepine
- Analgesics
  - Aspirin, ibuprofen, celecoxib, acetaminophen, phenylbutazone and oxyphenbutazone, naproxen, piroxicam, and chlormezanone (muscle relaxant)

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - FDE accounts for
    - 1% of drug eruptions among outpatients
    - 2-5% of drug eruptions among inpatients

### Presentation

- Initial solitary lesion typically on lips, genitalia, proximal extremity, hip, or lower back as oval erythematous patch, often with burning  $\pm$  itching
- Initial lesion may take up to 2 weeks to appear after drug exposure and fades over days to weeks with residual hyperpigmentation
- Subsequent episodes occur at same site with readministration of drug, each time, as well-defined oval hyperpigmented patch surrounded by rim of erythema
- Bullous lesions or erosions may occur (especially mucosal sites)

### Treatment

- Avoidance of causative agent
- Symptomatic treatment with topical corticosteroids and systemic antihistamines
- Desensitization to causative medication has been reported in literature, but avoidance is preferred

### Prognosis

- Lesions will recur until offending agent removed
- With repeated exposures, additional lesions may appear, along with reactivation of original lesion
  - Each of these will reactivate upon subsequent exposure to drug
  - Phenomenon is referred to as generalized FDE

## MICROSCOPIC

### Histologic Features

- Initial episode
  - Normal "basketweave" stratum corneum
  - Interface dermatitis with necrotic keratinocytes
  - Neutrophils &/or eosinophils in addition to lymphocytes
- Subsequent episodes
  - Normal "basketweave" stratum corneum
  - Interface dermatitis with necrotic keratinocytes
  - Neutrophils &/or eosinophils plus lymphocytes
  - Papillary dermal fibrosis
  - Pigment incontinence with melanophages around postcapillary venules

## DIFFERENTIAL DIAGNOSIS

### Urticarial Pemphigoid

- Shares acute (basketweave) stratum corneum and eosinophils at dermal-epidermal junction
- Lacks papillary dermal fibrosis and melanophages around postcapillary venules

### Erythema Annulare Centrifugum

- Superficial perivascular lymphoid infiltrate, focal spongiosis, and trailing parakeratotic scale

### Erythema Dyschromicum Perstans

- Atrophic lichenoid interface dermatitis with pigment incontinence

### Erythema Multiforme

- Acute (normal basketweave) stratum corneum with satellite necrosis of keratinocytes
- Lymphocytes only, with no eosinophils or neutrophils
- No papillary dermal fibrosis
- No pigment around postcapillary venules

### Acute Urticarial Reaction

- Neutrophils in lumina of postcapillary venules
- In later lesions, perivascular neutrophils and eosinophils without karyorrhexis
- No interface change
- No pigment incontinence

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# Lichenoid Drug Eruptions

## KEY FACTS

### TERMINOLOGY

- Drug reaction that simulates lichen planus histologically and clinically

### ETIOLOGY/PATHOGENESIS

- Causative agents include HMG-CoA reductase inhibitors, antitumor necrosis factor alpha inhibitors, beta blockers, angiotensin converting enzyme inhibitors, hydrochlorothiazide, antimalarials, and nonsteroidal antiinflammatory drugs

### CLINICAL ISSUES

- Individual lesions of lichenoid drug eruption resemble lichen planus but spare flexures and may be photodistributed

### MICROSCOPIC

- Differs from lichen planus by presence of parakeratosis, deep perivascular and periadnexal infiltrate, plasma cells, and eosinophils

### ANCILLARY TESTS

- Direct immunofluorescence is negative

### TOP DIFFERENTIAL DIAGNOSES

- Lichen planus
- Cutaneous lupus erythematosus
- Lichenoid contact dermatitis
- Cutaneous T-cell lymphoma

### DIAGNOSTIC CHECKLIST

- Photodistributed lichenoid drug eruption may be histologically indistinguishable from lichen planus

Psoriasiform Photodistributed Eruption



*Photodistributed lichenoid drug eruption is shown. The clinical appearance is psoriasiform but with histology of a lichenoid interface dermatitis with eosinophils. Recent ingestion of hydrochlorothiazide was noted.*



## TERMINOLOGY

### Abbreviations

- Lichenoid drug eruption (LDE)

### Synonyms

- Lichenoid drug reaction

### Definitions

- Drug reaction that simulates lichen planus (LP) histologically and clinically

## ETIOLOGY/PATHOGENESIS

### Drug Exposure

- Implicated drugs are numerous
  - HMG-CoA reductase inhibitors (statins)
  - Antitumor necrosis factor alpha inhibitors, such as adalimumab, imatinib
  - Antihypertensive medications including beta-blockers, angiotensin converting enzyme inhibitors, spironolactone, and thiazide diuretics, such as hydrochlorothiazide
  - Antimalarials
  - Glimepiride
  - Amalgam
  - Gold salts
  - Anticonvulsants, including carbamazepine and phenytoin
  - Antituberculous drugs, including streptomycin and isoniazid
  - Nonsteroidal antiinflammatory drugs
  - Antipsychotics
  - Methyldopa
  - Tetracyclines, such as demeclocycline and doxycycline
- Cytotoxic T-lymphocytes [CD8(+) lymphocytes] and NK cells are responsible for apoptosis underlying epidermal damage in LDE
  - Apoptosis is triggered by either extra- or intracellular mechanisms involving causative drug, and then these cells release toxic granules containing perforin and granzyme B
  - While interface dermatitis in LP and LDE are both due mainly to CD8(+) lymphocytes, this cytotoxicity is predominantly linked to granzyme B in LDE and to perforin in LP

## CLINICAL ISSUES

### Presentation

- Latency from drug introduction to onset of cutaneous manifestations in LDE is variable, from several weeks to 3 years
  - Resolution following withdrawal of offending agent can also take weeks to years
- Initially erythematous macules, which develop into flat-topped scaly violaceous papules, present symmetrically over trunk and limbs
- Wickham striae are usually absent, and flexures are typically spared, in contrast to LP
- Pruritus is common

- Although mucosal involvement has traditionally been considered rare in LDE, multiple reports, particularly those associated with beta-blocker therapy, describe oral or genital lesions
- Oral lichenoid reactions have been frequently reported due to contact with amalgam fillings, with resolution of clinical and histologic findings following removal
- LDE can be photodistributed, particularly when due to thiazide diuretics, antimalarials, and tetracyclines
- Additionally, LDE may demonstrate psoriasiform or eczematous morphologies
- Postinflammatory hyperpigmentation is often marked following resolution

### Treatment

- Drugs
  - In addition to cessation of causative drug, topical or oral corticosteroids have been used successfully

### Prognosis

- Resolution of lesions after removal of offending agent may be prompt or may take months to clear
- Postinflammatory hyperpigmentation can be marked and persistent

## MICROSCOPIC

### Histologic Features

- Nonphotodistributed LDE demonstrates lichenoid interface dermatitis with band-like infiltrate of lymphocytes, vacuolar degeneration, and superficial and deep perivascular and periadnexal lymphocytic infiltrate
- Sawtooth-like rete ridges, parakeratosis, and eosinophils are often present as well
- Photodistributed LDE may be histologically indistinguishable from LP
- Increased number of necrotic keratinocytes, grouped in clusters, exocytosis of lymphocytes, and plasma cells in dermal infiltrate are additional variable features

## ANCILLARY TESTS

### Immunofluorescence

- Typically direct immunofluorescence (DIF) is negative in LDE
- May be helpful finding in distinguishing LDE from LP and cutaneous lupus erythematosus (LE)

## DIFFERENTIAL DIAGNOSIS

### Lichen Planus

- Although no single histologic feature allows definitive distinction of LP from LDE, focal parakeratosis, interruption of granular layer, and cytooid bodies in cornified and granular layers favor diagnosis of LDE
- LP is less likely to demonstrate deep inflammation and eosinophils
- LP is more likely to demonstrate wedge-shaped hypergranulosis, melanophages in thickened papillary dermis, extravasated erythrocytes, and clefts at dermoepidermal junction
- DIF demonstrates ragged band of fibrinogen at dermoepidermal junction in nearly all cases along with variable IgM staining of cytooid bodies in papillary dermis

- Overall, distinction requires combination of historical, clinical, and histologic findings

## Cutaneous Lupus Erythematosus

- Epidermal atrophy, basement membrane thickening, and follicular plugging are absent in LDE
- While plasma cells are common to both disorders, eosinophils are absent in LE
- DIF can be helpful in distinction of LE from LP and LDE
  - DIF of lesional skin shows granular deposition of multiple reactants, with IgM most common and IgG 2nd most common
  - C3 is also deposited, paired with IgM

## Lichenoid Contact Dermatitis

- Overlapping clinical and histologic features are present, but lichenoid contact dermatitis may show subacute spongiosis and eosinophils in addition to lichenoid infiltrate
- Additionally, causative agents differ
  - Lichenoid contact dermatitis has been reported following exposure to color film developers, para-phenylenediamine, and chlorpheniramine

## Cutaneous T-Cell Lymphoma

- LDE can occasionally present with features of mycosis fungoides, but usually lymphocyte atypia and epidermotropism are lacking

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Parakeratosis
- Lichenoid interface dermatitis
- Superficial and deep perivascular and periadnexal lymphocytic infiltrate
- Plasma cells and eosinophils

### Pathologic Interpretation Pearls

- Photodistributed LDE may be indistinguishable from LP

## SELECTED REFERENCES

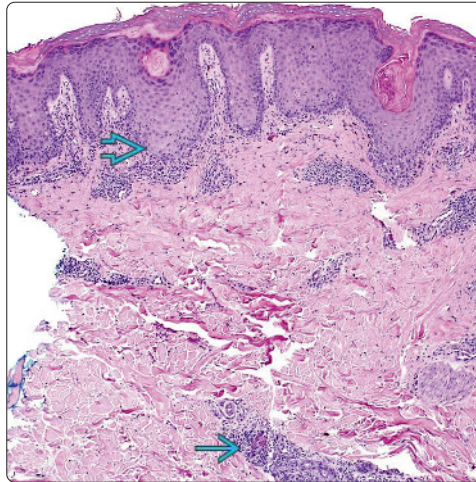
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**Diffuse Hyperpigmented Papules**

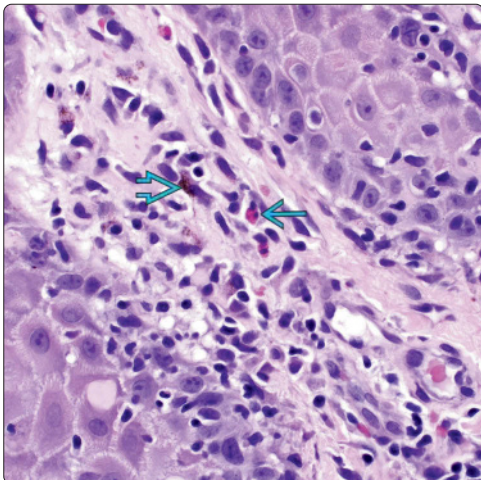


**Lichenoid Interface Dermatitis**

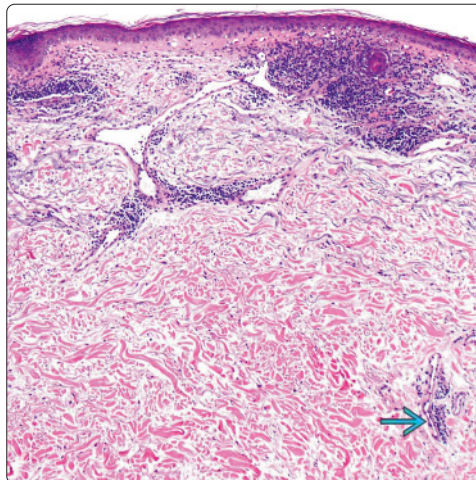


(Left) Lichenoid drug eruption shows diffuse hyperpigmented papules simulating lichen planus. (Courtesy S. Hsu, MD.) (Right) Lichenoid drug eruption shows lichenoid interface dermatitis with epidermal changes analogous to those seen in lichen planus. Note the presence of superficial and deep perivascular lymphocytic inflammation. (Courtesy S. Hsu, MD.)

**Pigment Incontinence and Eosinophils**

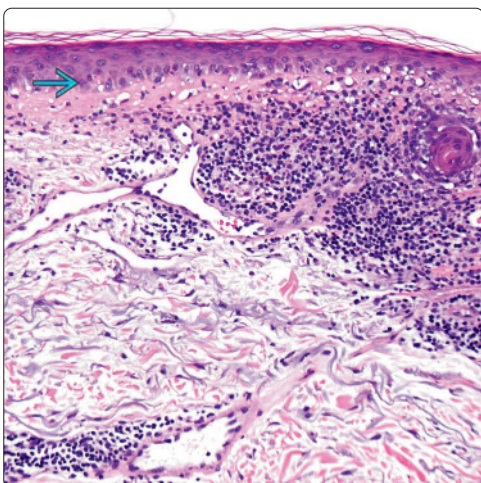


**Lichenoid Reaction Pattern With Superficial and Deep Inflammation**

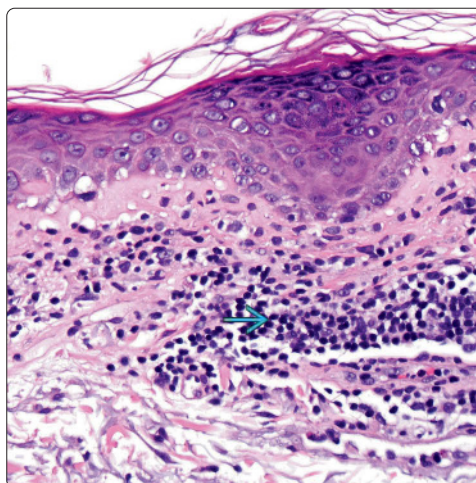


(Left) Pigment incontinence and numerous eosinophils are present. (Courtesy S. Hsu, MD.) (Right) Lichenoid drug eruption shows a lichenoid tissue reaction pattern with superficial and deep perivascular dermatitis on sun-damaged skin.

**Epidermal Atrophy With Vacuolar Alteration**



**Lymphoplasmacytic Inflammation**



(Left) Epidermal atrophy and vacuolar degeneration are seen in this example of a lichenoid drug eruption. (Right) A lichenoid drug reaction shows lymphoplasmacytic aggregates beneath a lichenoid interface dermatitis.



# Photodrug Eruptions

## KEY FACTS

### TERMINOLOGY

- Definition
  - Sunburn-like reaction due to photosensitizing agent and exposure to UVA that results in direct tissue damage

### CLASSIFICATION

- Exogenous photodermatoses, phytophotodermatoses

### CLINICAL ISSUES

- Typically presents on sun-exposed sites in lighter skinned persons who have been adequately exposed to sufficient doses of photosensitizing agent (often medication) and sun light

### MICROSCOPIC

- Epidermis has spongiosis, variable amounts of apoptotic keratinocytes a.k.a. sunburn cells, and variable amount of perivascular lymphocytic infiltrate

### TOP DIFFERENTIAL DIAGNOSES

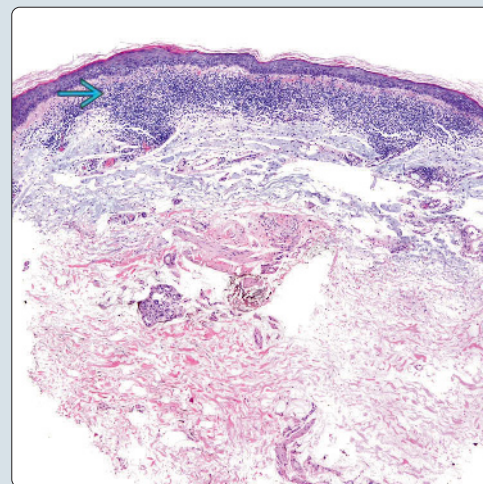
- Photoallergic
  - Can look more eczematous, lichenoid in nature and can affect nonsun-exposed skin after topical application of culprit
    - vs. phototoxic dermatitis, which is due more to systemic culprits on sun-exposed areas
  - Can have more prominent eosinophilic component
- Sunburn
  - Lacks topical or systemic medication history in susceptible persons
  - Can mimic phototoxic but lacks photosensitizing agent history

**Phototoxic Drug Reaction (Recall) to Methotrexate**

(Left) Sunburn-like reaction in a photodistribution in a patient previously on methotrexate. Note the well-defined borders of the affected area where the clothing stops [blue box]. (Right) A phototoxic drug reaction demonstrates at low power a lymphocytic band [blue box] within the superficial dermis.

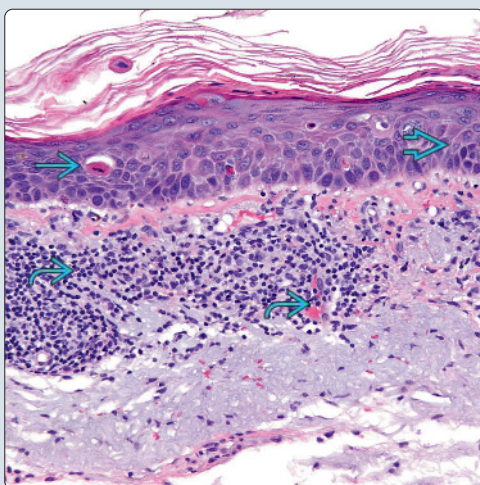


**Lymphocytic Band in Superficial Dermis**

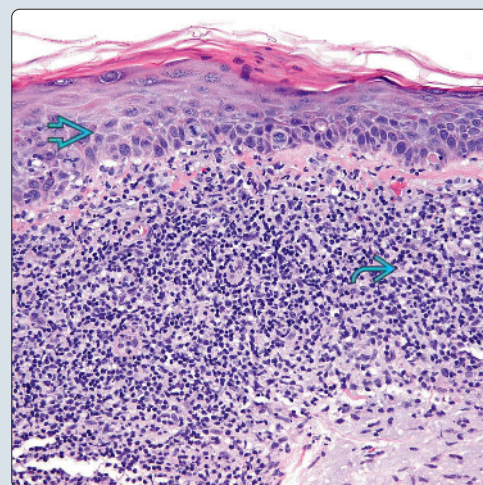


**Apoptotic Cells in Phototoxic Reaction**

(Left) Higher power H&E demonstrates apoptotic cells [blue box] and spongiosis [blue box] within the epidermis. Note the perivascular and band-like [blue box] infiltrate of lymphocytes. (Right) Higher power H&E demonstrates spongiosis [blue box] within the epidermis. Note the band-like [blue box] infiltrate of lymphocytes.



**Spongiosis and Lymphocytes Are Common**





## TERMINOLOGY

### Synonyms

- Phototoxic dermatitis
- Exogenous photodermatoses

### Definitions

- Sunburn-like reaction due to photosensitizing agent and exposure to UVA that results in direct tissue damage

## CLINICAL ISSUES

### Presentation

- Typically presents on sun-exposed sites in lighter skinned persons who have been adequately exposed to sufficient doses of photosensitizing agent (often medication) and sunlight
  - Frequently, following medications are culprits
    - Sulfonamides
    - Tetracyclines (doxycycline)
    - Furosemide
    - NSAIDs
    - Thiazides
    - Phenothiazines
    - Amiodarone
    - Antifungal agents (griseofulvin)
    - Antimetabolites (methotrexate)
  - Hyperpigmentation can last long time

### Treatment

- Options, risks, complications
  - Avoidance of photosensitizing agent and use of sun protection are critical

## MICROSCOPIC

### Histologic Features

- Epidermis has spongiosis and variable amounts of apoptotic keratinocytes a.k.a. "sunburn cells"
- Dermis contains variable amounts of perivascular lymphocytic infiltrates with lesser degrees of eosinophils and neutrophils

## DIFFERENTIAL DIAGNOSIS

### Clinical

- Photoallergic dermatitis
  - Can look more eczematous, lichenoid in nature and can affect nonsun-exposed skin after topical application of culprit
    - vs. phototoxic dermatitis, which is due more to systemic culprits on sun-exposed areas
- Sunburn
  - Lacks topical or systemic medication history in susceptible persons

### Histological

- Photoallergic dermatitis
  - Can have more prominent eosinophilic component
- Sunburn
  - Can mimic phototoxic but lacks photosensitizing agent history

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Typically presents on sun-exposed sites in lighter skinned persons who have been adequately exposed to sufficient doses of photosensitizing agent (often medication) and sunlight

### Pathologic Interpretation Pearls

- Epidermis has spongiosis and variable amounts of apoptotic keratinocytes a.k.a. "sunburn cells" with variable amounts of lymphocytic perivascular infiltrate

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## KEY FACTS

### TERMINOLOGY

- Dermatitis characterized by abnormal or exaggerated reaction to sunlight; caused by chemical photosensitizer
- Chemical photosensitizer may be encountered by topical application/contact or by ingestion

### ETIOLOGY/PATHOGENESIS

- Photosensitizing agents decrease threshold needed for induction of keratinocyte necrosis by solar radiation
  - Photosensitizers may be topically applied or introduced systemically (e.g., by ingestion)

### CLINICAL ISSUES

- Phototoxic dermatitis resembles sunburn, with blistering in severe cases
- Distribution corresponds to sun-exposed areas

### MICROSCOPIC





- Hallmark finding of phototoxic dermatitis is "sunburn cell" or necrotic keratinocyte

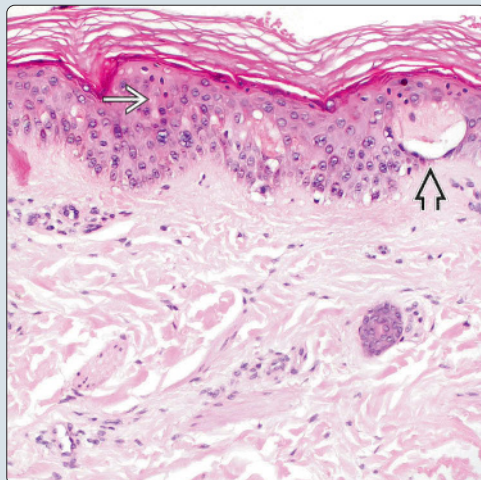
- Keratinocyte necrosis (individual cell dyskeratosis or confluent zones of necrosis)
- Inflammation by lymphocytes and neutrophils
- Papillary dermal edema may be present and, in extreme cases, can lead to subepidermal vesiculation

### TOP DIFFERENTIAL DIAGNOSES

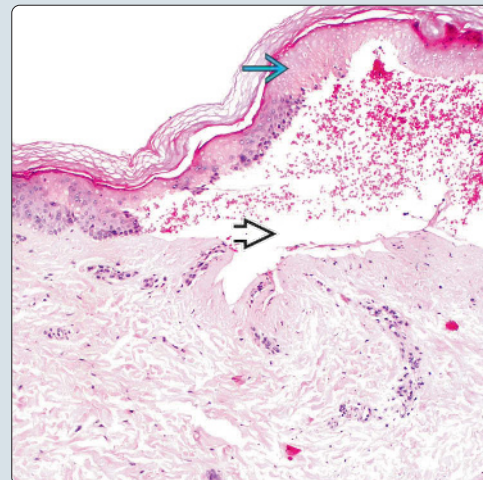
- Photoallergic dermatitis
  - Spongiosis with intraepidermal spongiotic vesiculation
  - Clinically distinguished by delay in onset following sun exposure as well as pruritus and eczematous change
- Toxic epidermal necrolysis
  - Confluent necrosis may resemble that seen in severe phototoxic dermatitis
- Drug eruption
  - Vacuolar interface dermatitis with scattered dyskeratotic keratinocytes
  - Dyskeratosis is less pronounced, and eosinophils may be seen

**Necrotic Keratinocytes With Confluence**




(Left) Individually, necrotic keratinocytes  are scattered in the epidermis. Dermal inflammation is sparse. Focal confluence of dyskeratosis leads to larger zones of necrosis . (Right) A severe phototoxic reaction with subepidermal blistering  and confluent epidermal necrosis overlying the blister  is shown.

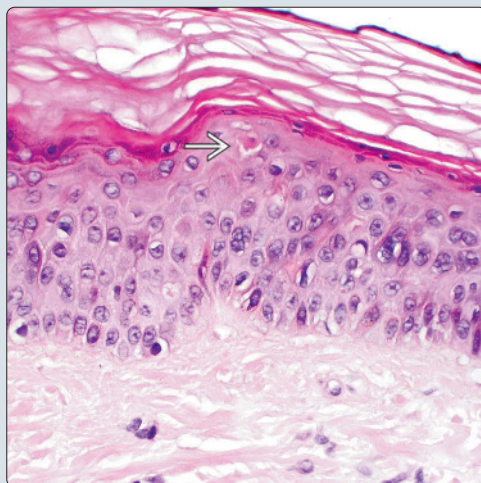


**Phytophotodermatitis With Subepidermal Blister and Epidermal Necrosis**

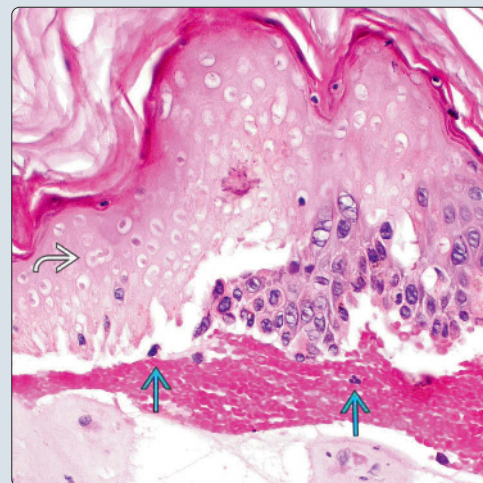


**Dyskeratotic Keratinocytes**

(Left) Scattered dyskeratotic keratinocytes are seen, some of which are present at higher levels in the epidermis . Inflammation is sparse. (Right) Near-complete epidermal necrosis is seen  with a subepidermal blister and a sparse inflammatory infiltrate with neutrophils .



**Epidermal Necrosis With Subepidermal Blister**





## TERMINOLOGY

### Synonyms

- Phytophotodermatitis: Phototoxic dermatitis secondary to contact with photosensitizing plant material
- Berloque dermatitis: Phototoxic dermatitis secondary to contact with photosensitizing chemicals; often cosmetics
- Phototoxic drug eruption: Phototoxic dermatitis secondary to ingestion of photosensitizing drug

### Definitions

- Dermatitis characterized by abnormal or exaggerated reaction to sunlight, caused by chemical photosensitizer
  - Chemical photosensitizer may be encountered by topical application/contact or by ingestion

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- Photosensitizing chemicals decrease threshold for induction of keratinocyte necrosis following exposure to solar ultraviolet radiation
- Reaction is nonimmunologically mediated
- Associated with systemic medications including psoralens, tetracyclines, fluoroquinolones, NSAIDs, voriconazole, multikinase inhibitors, and many others
- Topical photosensitizers include plants (bergamot, lime, fig, parsnip), cosmetics, coal tar, drugs (NSAIDs, retinoids)

## CLINICAL ISSUES

### Presentation

- Symmetric distribution predominating in sun-exposed areas (face, V of neck, dorsal arms and hands)
- Reaction resembles sunburn: Tenderness, erythema, blistering, and erosions
  - Severity of reaction depends on dose of photosensitizer and intensity/duration of sun exposure
  - Erythema begins within 4-6 hours of sun exposure and worsens in crescendo fashion over next 2-3 days
  - Photo-onycholysis: Detachment of nail plate from nail bed following sun exposure
    - Typically associated with chemotherapy agents and tetracycline antibiotics
  - Healing phase may result in postinflammatory hyperpigmentation

### Treatment

- Options, risks, complications
  - Discontinuation of sun exposure and identification/avoidance of photosensitizing agents
    - Phototesting and photopatch testing can help identify potential sensitizers
  - Topical application of bland emollients or steroid ointments
  - Oral corticosteroids in severe cases

### Prognosis

- Dermatitis is self-limited
- Risk of recurrence depends on ability to identify and avoid photosensitizer
- Healed lesions may show hyperpigmentation

## MICROSCOPIC

### Histologic Features

- Hallmark finding of phototoxic dermatitis is "sunburn cell" or necrotic keratinocyte
- Necrotic keratinocytes may be found as scattered individual cells (dyskeratosis) or as confluent zones of necrosis
  - When confluence of necrosis is seen, epidermis may detach from dermis
- Ballooning degeneration leads to pallor and intraepidermal vesiculation
- Spongiosis and exocytosis of inflammatory cells including lymphocytes and neutrophils
- Papillary dermal edema may be present and, in extreme cases, can lead to subepidermal vesiculation

## DIFFERENTIAL DIAGNOSIS

### Histopathologic Differential Diagnosis

- Photoallergic dermatitis
  - Spongiosis with intraepidermal spongiotic vesiculation
  - Perivascular infiltrate of lymphocytes and eosinophils; may also see eosinophils in epidermis
- Toxic epidermal necrolysis
  - Confluent necrosis may resemble that seen in severe phototoxic dermatitis
- Drug eruption
  - Vacuolar interface dermatitis with scattered dyskeratotic keratinocytes
  - Dyskeratosis is less pronounced, and eosinophils may be seen

### Clinical Differential Diagnosis

- Photoallergic dermatitis
  - Immunologically mediated hypersensitivity or contact dermatitis with induction or exacerbation by sun exposure
  - Clinically distinguished by delay in onset following sun exposure as well as pruritus and eczematous change
  - More frequently caused by topical agents than by ingestion of sensitizing drug
- Polymorphous light eruption
  - Mildly pruritic grouped pink papules on sun-exposed skin
  - Delayed onset (1-2 days) following sun exposure
  - Usually follows seasonal course with highest incidence in spring and early summer
- Solar urticaria
  - Transient urticarial plaques develop within minutes of sun exposure and resolve spontaneously

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5. Yashar SS et al: Classification and evaluation of photodermatoses. *Dermatol Ther.* 16(1):1-7, 2003

## Acute Generalized Exanthematous Pustulosis

## KEY FACTS

## TERMINOLOGY

- Sudden onset of numerous, small, nonfollicular pustules superimposed on pruritic, edematous erythroderma with spontaneous resolution followed by desquamation

## ETIOLOGY/PATHOGENESIS

- Associated with drugs, viral infections, and mercury
- Wide variety of other medications have also been implicated

## CLINICAL ISSUES

- Pustular eruption begins on face or intertriginous regions and becomes generalized with spontaneous resolution and subsequent desquamation
- Facial edema, purpura, vesicles, blisters, and erythema multiforme-like lesions have been reported
- Mucous membranes affected in few patients
- Pyrexia usually present
- Laboratory findings

- Peripheral leukocytosis with elevated neutrophil counts and eosinophilia can be present

## MICROSCOPIC

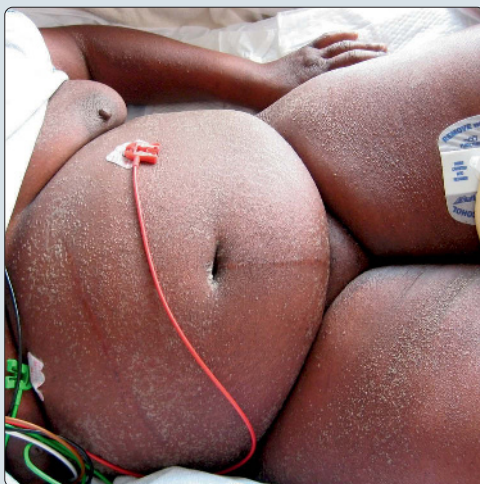
- Subcorneal &/or intraepidermal pustules
- Variable acantholysis
- May have leukocytoclastic vasculitis
- Perivascular lymphocytes, neutrophils, and sometimes rare eosinophils

## TOP DIFFERENTIAL DIAGNOSES

- Subcorneal pustular dermatosis (Sneddon-Wilkinson)
- Pustular psoriasis
- Pustular vasculitis
- Sweet syndrome
- Anticonvulsant hypersensitivity syndrome
- Drug rash with eosinophilia and systemic symptoms
- Toxic epidermal necrolysis

## Widespread White Pustules

**(Left)** Acute generalized exanthematous pustulosis (AGEP) appears as innumerable 1- to 3-mm white pustules and can appear anywhere on the body. This patient has involvement of extremities as well as the trunk. **(Right)** As the numerous white pustules begin to resolve, widespread desquamation occurs. Some white pustules are still present in the lower portion of the photo.

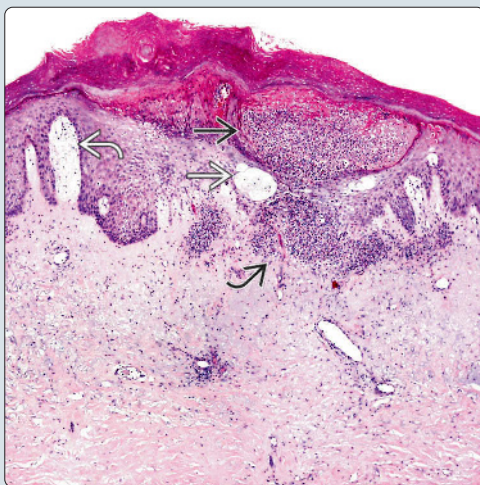


## Widespread Desquamation

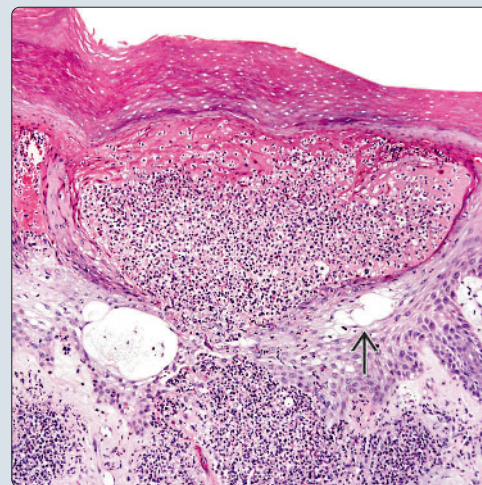


## Subcorneal Pustule

**(Left)** AGEP classically presents as a subcorneal pustule filled with neutrophils, mild to marked spongiosis, a mixed superficial dermal inflammatory infiltrate, and papillary dermal edema. **(Right)** AGEP can appear very similar histologically to both subcorneal pustular dermatosis and pustular psoriasis. Papillary dermal edema, spongiosis, and eosinophils within the superficial dermal infiltrate favor AGEP.



## Subcorneal Pustule With Spongiosis





## TERMINOLOGY

### Abbreviations

- Acute and generalized exanthematous pustulosis (AGEP)

### Synonyms

- Generalized toxic pustuloderma, pustular drug eruption, generalized pustular dermatosis

### Definitions

- Acute onset of numerous, small, sterile, nonfollicular pustules superimposed on pruritic, edematous erythroderma that spontaneously resolves and is followed by diffuse desquamation

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- May develop as consequence of mercury toxicity

### Infectious Agents

- Viruses, specifically enteroviruses, and spider bites have been offenders

### Antibacterial Antibiotic Therapy

- Pristinamycin, penicillin, amoxicillin, ampicillin, metronidazole, trimethoprim, and erythromycin

### Other Medications

- Analgesics (acetaminophen), antiepileptics (carbamazepine), antidiabetics (carbutamide), antifungals (terbinafine), antimalarials (hydroxychloroquine), and wide variety of others have been implicated

## CLINICAL ISSUES

### Presentation

- Pustular eruption typically begins on face or intertriginous regions and rapidly becomes generalized
  - Usually begins within hours of exposure to causative agent
  - Eruption resolves and is followed by widespread desquamation
- Facial edema, purpura, vesicles, blisters, and erythema multiforme-like lesions have been reported
- Mucous membranes affected in few patients
- Pyrexia usually present

### Laboratory Tests

- Peripheral leukocytosis with elevated neutrophil counts and eosinophilia can be present

### Prognosis

- Usually benign, self-limited course after cessation of offending agent

## MICROSCOPIC

### Histologic Features

- Subcorneal &/or intraepidermal pustules
  - Variable acantholytic keratinocytes and neutrophils
  - Background of spongiosis common
- Perivascular lymphohistiocytic infiltrate with scattered neutrophils and rare eosinophils is generally present in superficial dermis

- Leukocytoclastic vasculitis in significant proportion of cases

## DIFFERENTIAL DIAGNOSIS

### Histological

- **Subcorneal pustular dermatosis (Sneddon-Wilkinson)**
  - Subcorneal pustules with neutrophils and fibrin that sit at base of blister ("half and half" blister seen clinically)
- **Pustular psoriasis**
  - Dermal perivascular infiltrate composed of neutrophils and lymphocytes with subcorneal neutrophilic pustule
  - May show aggregates of neutrophils between thinned, degenerated keratinocytes (spongiform pustules of Kogoj)
  - Psoriasiform hyperplasia in older lesions
- **Pustular vasculitis**
  - Bullous &/or small pustular lesions localized to dorsal hands and may be drug induced

### Clinical

- **Pustular psoriasis (von Zumbusch type)**
  - More chronic course than AGEP
  - Pustules indistinguishable from AGEP
  - Must be distinguished histologically
- **Subcorneal pustular dermatosis (Sneddon-Wilkinson)**
  - Vesicles and pustules in circular plaques in skin folds
  - Blisters larger and more flaccid than in AGEP
  - Far less acute in evolution than AGEP
- **Toxic epidermal necrolysis**
  - AGEP pustules may coalesce and give false-positive Nikolsky sign
  - Epidermal sloughing and mucous membrane involvement more prominent in toxic epidermal necrolysis
- **Anticonvulsant hypersensitivity syndrome**
  - Secondary to anticonvulsant medications
  - Severe morbilliform rash with fever and lymphadenopathy
- **Sweet syndrome**
  - Erythematous plaques rather than pustules on face, neck, and arms
  - Mucositis common
- **Drug rash with eosinophilia and systemic symptoms**
  - May present with papulopustules but less pronounced pustules
  - Fever, lymphadenopathy, eosinophilia, and multiorgan involvement

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# Drug Rash With Eosinophilia and Systemic Symptoms

## KEY FACTS

### TERMINOLOGY

- Rare, potentially life-threatening syndrome, including severe eruption, fever, hypereosinophilia, and multiorgan toxicity

### ETIOLOGY/PATHOGENESIS

- Main culprit drugs are carbamazepine and allopurinol

### CLINICAL ISSUES

- Drug rash with eosinophilia and systemic symptoms (DRESS) is difficult to diagnose, as it mimics many other serious systemic disorders
- Eruption begins with erythematous papules on trunk that eventually become confluent and develop into maculopapular or erythrodermatous eruption
  - Mucous membranes spared
- Mortality rate is up to 20% in those who develop hepatitis

### MICROSCOPIC

- Histopathologic features are that of morbilliform drug eruption and are not specific for DRESS
  - Small foci of spongiosis with vacuolization of dermal-epidermal junction with scattered apoptotic cells
  - Sparse, perivascular inflammatory infiltrate consisting of activated lymphocytes, macrophages, mast cells, and occasional eosinophils
    - Eosinophils may be absent

### ANCILLARY TESTS

- DRESS can be associated with human herpesvirus 4, 6, and 7 infections; thus, serology of these viruses should be checked

### TOP DIFFERENTIAL DIAGNOSES

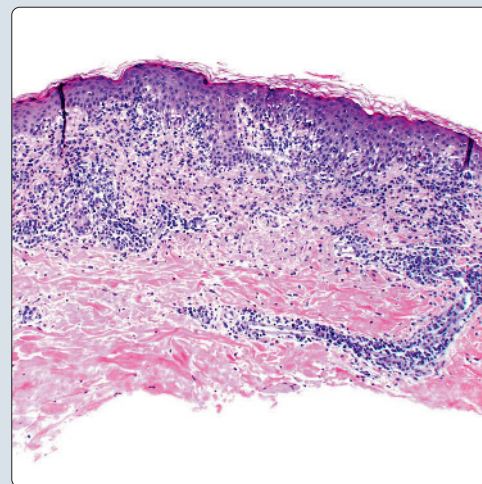
- Fixed drug eruption, exanthematous drug reaction, photosensitive drug eruption, lichenoid drug eruption, erythema multiforme

### Erythematous Papules

(Left) The eruption of drug rash with eosinophilia and systemic symptoms (DRESS) begins with erythematous papules on trunk [A] that eventually become confluent and develop into a maculopapular or erythrodermatous eruption. (Courtesy D. Cassarino, MD, PhD.) (Right) DRESS shows an interface dermatitis and vacuolar degeneration of the dermal-epidermal junction as well as a mixed dermal inflammatory infiltrate. (Courtesy D. Cassarino, MD, PhD.)

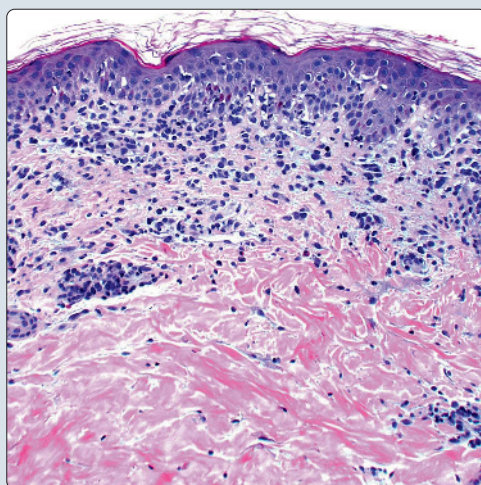


### Interface Dermatitis

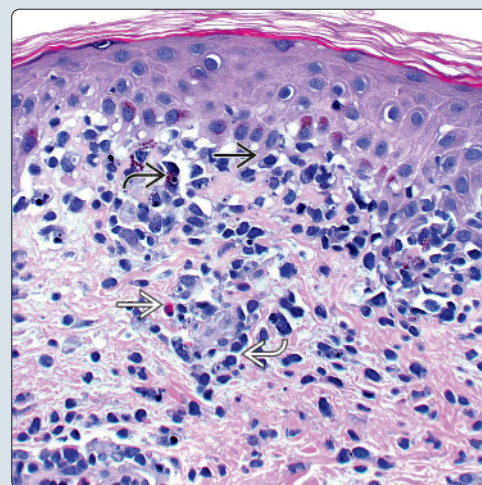


### Vacuolar Degeneration and Perivascular Infiltrate

(Left) DRESS shows minimal spongiosis with exocytosis, vacuolar degeneration of the basal layer, and a perivascular lymphocytic infiltrate with eosinophils. (Courtesy D. Cassarino, MD, PhD.) (Right) DRESS shows vacuolar degeneration of the basal layer [A] with dermal melanophages [B], eosinophils [C], and perivascular lymphocytic inflammation [D]. (Courtesy D. Cassarino, MD, PhD.)



### Vacuolar Degeneration, Melanophages, Eosinophils and Lymphocytes





## TERMINOLOGY

### Abbreviations

- Drug rash with eosinophilia and systemic symptoms (DRESS)

### Synonyms

- Drug-induced delayed multiorgan system hypersensitivity syndrome

### Definitions

- Rare, life-threatening, drug-induced hypersensitivity syndrome characterized by severe skin eruption, fever, hematologic abnormalities (eosinophilia or atypical lymphocytes), and internal organ involvement

## ETIOLOGY/PATHOGENESIS

### Etiology

- Potentiated by numerous drugs (~ 50)
  - Most common medications include minocycline, allopurinol, sulfonamides, phenytoin, phenobarbital, and carbamazepine

### Pathogenesis Is Partially Understood

- Detoxification defects leading to reactive metabolite formation and subsequent immunological reactions, slow acetylation, and reactivation of human herpes, including Epstein-Barr virus and human herpesvirus (HHV)-6 and HHV-7, as well as CMV
- Detection of HHV-6 reactivation has even been recently proposed as diagnostic marker for DRESS

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Estimated incidence is 1 in 1,000 to 1 in 10,000 drug exposures
- Sex
  - No gender predilection
- Ethnicity
  - Predominantly described in African American patients

### Presentation

- Eruption begins with erythematous papules on trunk that eventually become confluent and develop into maculopapular or erythrodermatous eruption
  - Mucous membranes spared
- Additional signs/symptoms
  - Facial or periorbital edema, strawberry tongue, conjunctivitis, &/or pharyngitis
  - Tender lymphadenopathy, myositis, hepatitis
  - Renal, pulmonary (interstitial pneumonitis), and hematologic (atypical lymphocytosis) manifestations may occur
- Delayed onset, usually 1-8 weeks after initiation of drug therapy
- Possible persistence or aggravation of symptoms despite discontinuation of culprit drug

### Treatment

- Withdrawal of culprit drug
- Corticosteroid treatment

### Prognosis

- Mortality rate is up to 20% in those who develop hepatitis

## MICROSCOPIC

### Histologic Features

- Histopathologic features are that of morbilliform drug eruption and are not specific for DRESS
  - Small foci of spongiosis with vacuolization of dermal-epidermal junction with scattered apoptotic cells
  - Sparse, perivascular inflammatory infiltrate consisting of activated lymphocytes, macrophages, mast cells, and occasional eosinophils
  - Papillary dermis may be edematous and show vascular dilatation
  - Eosinophils may be absent
  - Epidermal changes are typically minimal or absent

### Cytologic Features

- Lymphocytes may appear larger, suggesting activation

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Fixed drug eruption
  - More significant basal cell hydropic degeneration with lymphocyte tagging along dermal-epidermal junction and keratinocyte necrosis
  - More abundant pigment incontinence than in DRESS
- Exanthematous drug reaction
  - Less interface changes than DRESS, with focal spongiosis and mild exocytosis of lymphocytes
  - More Civatte bodies (apoptotic keratinocytes) in basal layer than in DRESS
- Photosensitive drug eruption
  - Rare apoptotic keratinocytes, solar elastosis, and stellate fibroblasts are seen
- Lichenoid drug eruption
  - Similar interface dermatitis as in DRESS, but melanin incontinence and eosinophils are not characteristically seen
- Erythema multiforme
  - Milder lichenoid infiltrate than in DRESS and many more apoptotic keratinocytes

### Clinical

- Erythema multiforme
  - Targetoid lesions rather than diffuse rash in most cases, with predilection for palms and soles
- Toxic epidermal necrolysis
  - Large flaccid bullae with subsequent widespread skin sloughing
- Vasculitis
  - Palpable purpura are seen, usually on lower extremities
- Viral exanthem
  - Diffuse morbilliform rash but with multiple constitutional symptoms (fever, chills, headache, etc.) and viral illness

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# Toxic Erythema of Chemotherapy

## KEY FACTS

### TERMINOLOGY

- Many synonyms, including acral erythema, epidermal dysmaturation, erythrodysesthesia, hand-foot syndrome, eccrine squamous syringometaplasia
- Toxic erythema of chemotherapy is inclusive term encompassing many different clinical presentations of chemotherapy reactions

### ETIOLOGY/PATHOGENESIS

- Most common causes: Cytarabine, doxorubicin, 5-fluorouracil, capecitabine, docetaxel, paclitaxel, methotrexate

### CLINICAL ISSUES

- Symmetric erythematous eruptions
- Most often on palms and soles
- Usually painful or burning
- May also involve intertriginous zones
- Eruptions occur 2-3 weeks after initiation of chemotherapy



- Eruptions resolve spontaneously once chemotherapy stops

### MICROSCOPIC

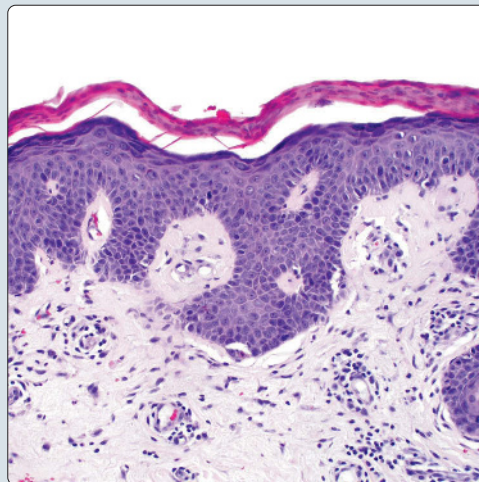
- Vacuolar alteration
- Individually necrotic keratinocytes
- Sparse inflammation
- Keratinocyte atypia
- Frequent mitoses
- Epidermal dysmaturation: Crowding and loss of polarity
- Squamous metaplasia of eccrine sweat duct

### TOP DIFFERENTIAL DIAGNOSES

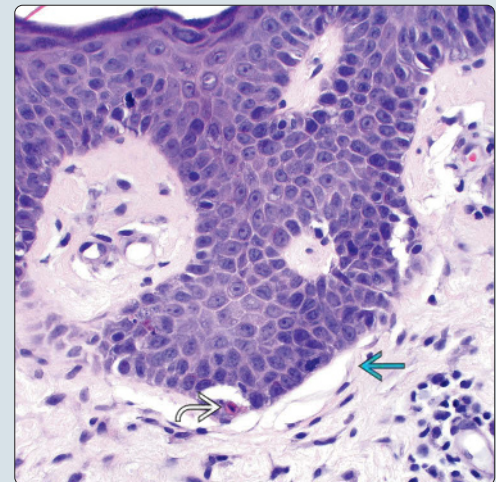
- Erythema multiforme
- Stevens-Johnson syndrome
- Graft-vs.-host disease
- Morbilliform drug eruption




(Left) A low-power view of toxic erythema of chemotherapy demonstrates a perivascular mononuclear infiltrate and dilated blood vessels. (Right) The epidermis is crowded with keratinocytes, and there is vacuolar alteration  along the epidermal basement membrane. Individually, necrotic keratinocytes  are seen in the basal layer as well.

Mononuclear Perivascular Infiltrate

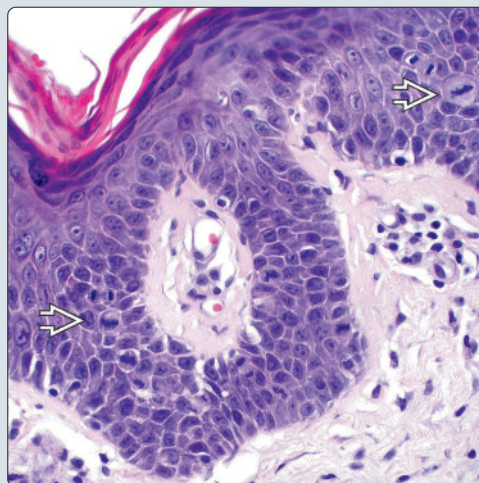


Vacuolar Alteration and Necrotic Keratinocytes

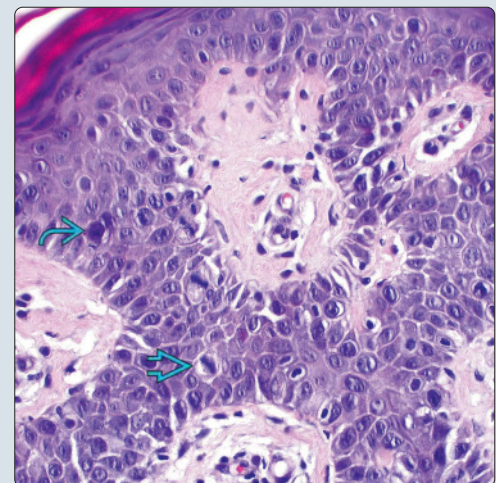


(Left) Chemotherapy agents cause keratinocytes to arrest in mitosis within the epidermis. Mitotic figures  are conspicuous, including some in the suprabasilar epidermis. (Right) Scattered cytologic atypia  as well as basilar and suprabasilar mitotic figures  are typical of toxic erythema of chemotherapy.

Keratinocytes in Mitotic Arrest



Cytologic Atypia and Scattered Mitotic Figures





## TERMINOLOGY

### Synonyms

- Acral erythema, epidermal dysmaturation, erythrodysesthesia, hand-foot syndrome, eccrine squamous syringometaplasia

### Definitions

- Painful erythematous eruption secondary to administration of chemotherapy agents

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- Chemotherapeutic agents, including cytarabine, doxorubicin, 5-fluorouracil, capecitabine, docetaxel, paclitaxel, methotrexate

## CLINICAL ISSUES

### Presentation

- Symmetric erythema and edema
  - Symptoms include pain, burning, or pruritus
- Predominates on acral skin (palms and soles), where eccrine glands are dense
- May also affect intertriginous areas, ears, nose, extremities
- May blister
- Desquamation is common
- Eruptions occur 2-3 weeks after initiation of chemotherapy

### Treatment

- Options, risks, complications
  - Most treatments are nonspecific and aim to alleviate symptoms
  - May treat with cool compresses, pain medications, topical steroids, or emollients

### Prognosis

- Lesions tend to desquamate then heal spontaneously
- May hyperpigment
- Usually will recur if patient is reexposed to same chemotherapy

## MICROSCOPIC

### Histologic Features

- Keratinocytes frequently show cytologic atypia
  - Enlarged nuclei
  - Nuclear pleomorphism
  - Hyperchromatism
- Keratinocytes arrested in mitosis
  - Basilar and suprabasilar mitoses common
  - Mitoses may have bizarre forms
  - Ring mitoses characteristic of taxane therapy
- Crowding of keratinocytes within epidermis and loss of polarity ("epidermal dysmaturation")
- Vacuolar interface alteration
- Individually necrotic keratinocytes
  - Severe cases may show more confluent or widespread necrosis of upper levels of epidermis
- Papillary dermal edema
- Sparse perivascular infiltrate of mononuclear cells
- Squamous metaplasia of eccrine sweat ducts

- May see dyskeratosis within eccrine epithelium
- Papillary dermal melanophages in long-standing lesions

### Cytologic Features

- Nuclear pleomorphism and frequent mitoses

## DIFFERENTIAL DIAGNOSIS

### Graft-vs.-Host Disease

- Distribution is more widespread
- May be morbilliform or lead to blistering
- Patients usually have diarrhea and acute hepatitis
- Histologically shows vacuolar interface dermatitis with individually necrotic keratinocytes
- May have full-thickness epidermal necrosis
- Lacks keratinocyte atypia and mitoses

### Erythema Multiforme/Stevens-Johnson Syndrome

- Usually has acral target lesions
- Involves mucosal surfaces
- Limited epidermal detachment
- Has vacuolar interface change with individually necrotic keratinocytes
- Lacks keratinocyte atypia and mitoses

### Morbiliform Drug Eruption

- Pink to red macules and papules
- Predominantly on trunk
- No blistering
- Shows vacuolar alteration with rare dyskeratosis
- Lacks keratinocyte atypia and mitoses

### Contact Dermatitis

- Usually pruritic but not painful
- Distribution is determined by pattern of allergen contact
- Epidermal spongiosis
- May see eosinophils
- Lacks keratinocyte atypia or mitoses

### Squamous Cell Carcinoma In Situ

- Single lesion rather than widespread eruption
- More diffuse keratinocyte atypia and bizarre mitoses
- Parakeratosis
- Sun-damaged skin

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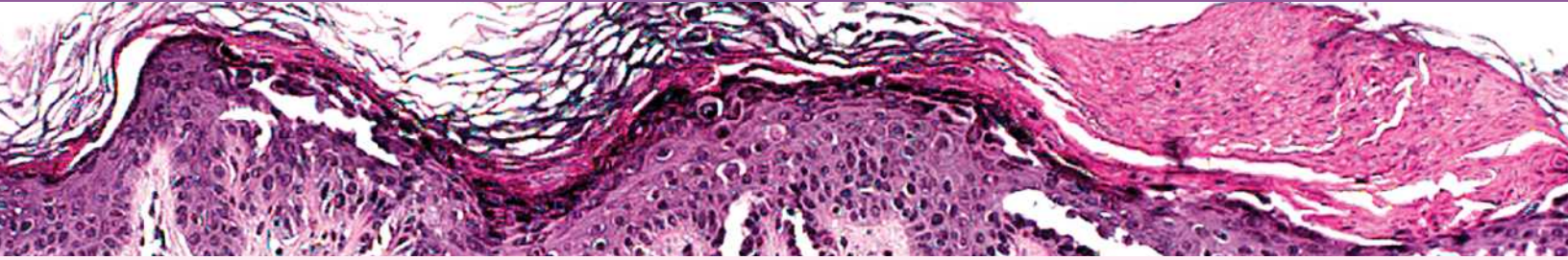
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## SECTION 14

# Disorders of Epidermal Maturation and Keratinization



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## Grover Disease

## KEY FACTS

## TERMINOLOGY

- Pruritic, papulovesicular dermatosis of trunk, mostly in middle-aged men, with histology characterized by focal acantholysis, dyskeratosis, and clefting

## CLINICAL ISSUES

- Extremely pruritic, discrete, round, erythematous or skin-colored papules and papulovesicles, found primarily on upper and mid trunk
- Mostly Caucasian men in 5th-6th decades
- Transient or chronic course
- UV exposure, sweating, heat, friction, radiation therapy, and xerosis exacerbate eruption

## MICROSCOPIC

- 4 histological patterns: Darier-like, Hailey-Hailey-like, pemphigus vulgaris-like, and spongiotic
  - Focal acantholysis, dyskeratosis, and clefting
  - Superficial perivascular lymphocytic infiltrates

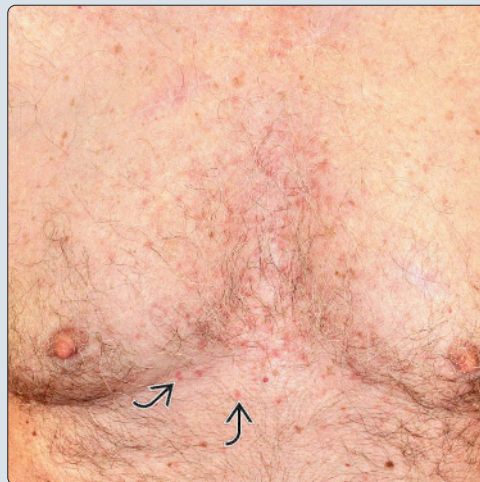
- Biopsy specimen tends to demonstrate > 1 histological pattern
- Eosinophils may be seen, which is distinguishing feature from Darier disease

## DIAGNOSTIC CHECKLIST

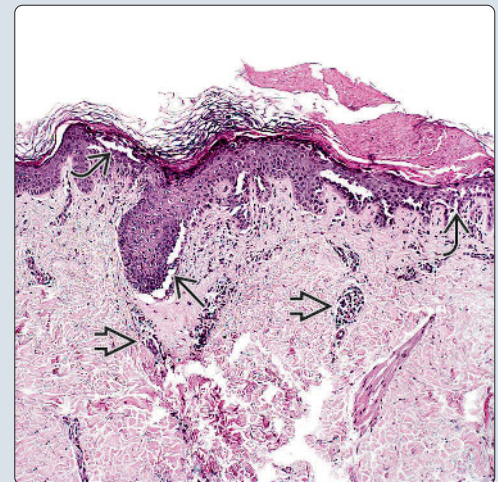
- Clinical features
  - Pruritic, discrete, small papulovesicles, found primarily on trunk
  - Chiefly on central chest and middle back in middle-aged Caucasian men
- Pathologic interpretation pearls
  - Histologically, it may be difficult to distinguish Grover disease from other acantholytic diseases, such as Darier disease, Hailey-Hailey disease, and pemphigus; hence clinicopathologic correlation is important

## Nonfollicular-Based Papules

(Left) Grover disease (GD) presented as discrete, erythematous or skin-colored, nonfollicular-based pink papules and papulovesicles on the central chest of this middle-aged man. (Courtesy J. Chan, MD.) (Right) GD demonstrates focal acantholysis, dyskeratosis, clefting, and superficial perivascular lymphocytic infiltrates. Clinicopathologic correlation is important to distinguish GD from other acantholytic diseases.



## Focal Areas of Acantholysis



## Nonfollicular-Based Pink Papules

(Left) GD presents as 1- to 2-mm discrete, erythematous, nonfollicular-based pink papules and papulovesicles on the central chest, middle back, and occasionally elsewhere. (Courtesy K. Kia, MD.) (Right) The papules are commonly excoriated, crusted, or eroded because the eruptions are extremely pruritic. Exacerbation factors include sun exposure, sweating, heat, friction, ionizing radiation, and xerosis.



## Crusting Is Common





**TERMINOLOGY****Abbreviations**

- Grover disease (GD)

**Synonyms**

- Transient acantholytic dermatosis (TAD), persistent acantholytic dermatosis, benign papular acantholytic dermatosis

**Definitions**

- Pruritic, papulovesicular dermatosis of trunk, mostly in middle-aged men, with histology characterized by focal acantholysis, dyskeratosis, and clefting

**ETIOLOGY/PATHOGENESIS****Unknown**

- Exacerbation factors include sun exposure, sweating, heat, friction, ionizing radiation, and xerosis
- Certain drugs, such as IL-4, ribavirin, d-penicillamine, and other chemotherapeutic agents, may precipitate GD
- Common in winter months

**CLINICAL ISSUES****Epidemiology**

- Age
  - Mostly in middle-aged to elderly men (40s-50s)
- Sex
  - Male
- Ethnicity
  - Caucasian

**Presentation**

- Pruritic
- Sudden onset is common
- 1- to 2-mm discrete, erythematous, or skin-colored nonfollicular round papules and papulovesicles
- Chiefly on central chest, middle back, and occasionally elsewhere
- Commonly excoriated, crusted, or eroded

**Prognosis**

- Varies
  - TAD may resolve in weeks to months, or may have chronic relapsing course over period of years

**MACROSCOPIC****General Features**

- Discrete, small, round papules and papulovesicles

**MICROSCOPIC****Histologic Features**

- Primary features are focal acantholysis and dyskeratosis resulting in intraepidermal clefting and vesicle formation
- 4 histological patterns
  - Darier-like
    - Various degree of keratin plugging and hyperkeratosis
    - Suprabasal cleft formation and acantholysis
    - Dyskeratotic changes, including corps ronds and grains

- Hailey-Hailey-like
  - Broad full thickness epidermal acantholysis
  - Dilapidated brick wall appearance
- Pemphigus vulgaris-like
  - Suprabasal cleft formation and acantholysis
  - Tombstone appearance
- Spongiotic
  - Various degrees of epidermal spongiosis
  - Various degrees of acantholytic changes
- All patterns demonstrate mild to moderate superficial perivascular lymphocytic infiltrate
- Biopsy specimen tends to demonstrate > 1 histological pattern
- Eosinophils sometimes present, which is distinguishing feature between GD and Darier disease

**DIFFERENTIAL DIAGNOSIS****Histopathologic**

- Diseases with acantholytic features
  - Histologically, all of these diseases below may not be distinguished from GD, but clinically they are easily recognizable
    - In GD, biopsy specimen demonstrates > 1 histological pattern
  - Darier disease: Predominantly dyskeratosis with acantholysis
  - Hailey-Hailey disease: Dilapidated brick wall
  - Pemphigus vulgaris: Tombstoning of basilar keratinocytes
  - Focal acantholytic dyskeratosis: More focal and subtle
  - Warty dyskeratoma: Cup-shaped invagination or acanthosis

**DIAGNOSTIC CHECKLIST****Clinically Relevant Pathologic Features**

- Extremely pruritic, discrete, round, erythematous papules and papulovesicles, found primarily on upper and mid trunk in middle-aged Caucasian men

**Pathologic Interpretation Pearls**

- Focal acantholysis and clefting
- Biopsy specimen demonstrates > 1 histological pattern

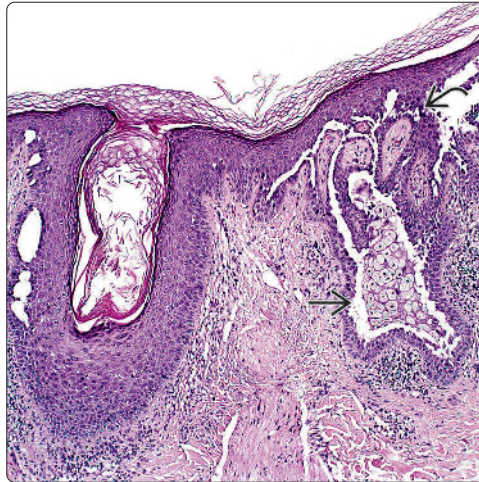
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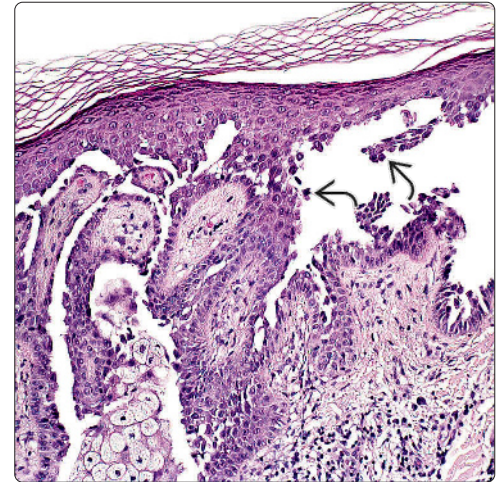
## Grover Disease

Pemphigus-Like Pattern

(Left) Pemphigus-like pattern of GD demonstrates suprabasal cleft formation [A], acantholysis [B], and characteristic tombstone appearance. Note the small skip lesions. Each lesion demonstrates focal acantholysis and clefting. (Right) The characteristic tombstone appearance is shown. Degenerative acantholytic cells [C] are floating in clefting spaces. Dyskeratotic changes are not common.



Tombstone Pattern

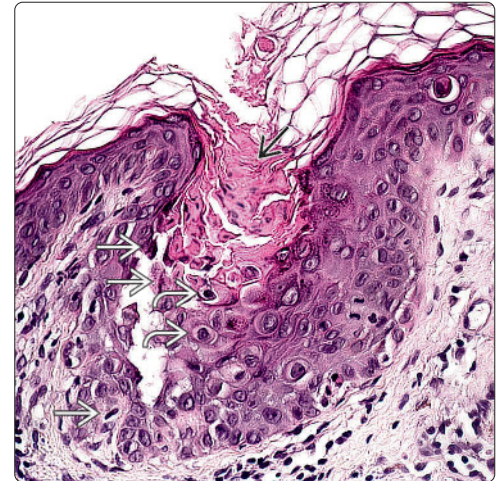


Darier-Like Dyskeratosis

(Left) Darier-like pattern of GD demonstrates acanthosis [A], thickened cornified layer [B], suprabasal cleft formation, acantholysis, and dyskeratotic cells in the epidermis. Superficial, mild, perivascular lymphocytic infiltrate is seen. (Right) Keratin plug [C], acanthosis, and dyskeratotic cells, such as corps ronds [D] and grains [E], are seen in the epidermis. Eosinophils may also be seen and are a distinguishing feature of GD from Darier disease, in which eosinophils are not normally seen.

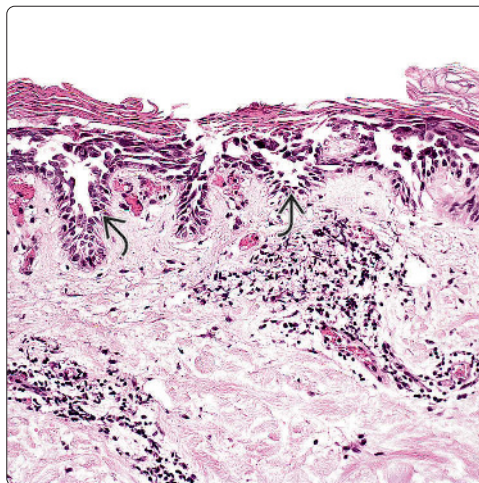


Corp Ronds and Grains

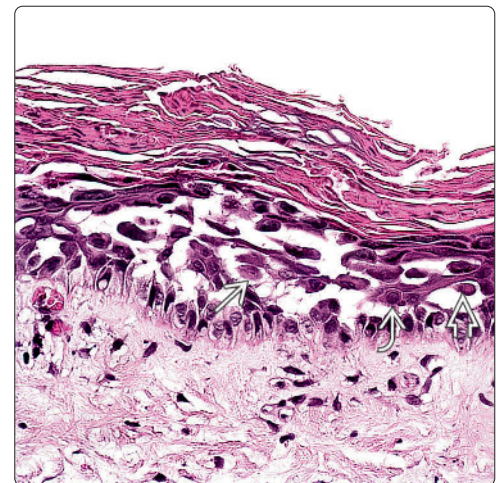


Hailey-Hailey-Like Pattern

(Left) Hailey-Hailey-like pattern shows suprabasal acantholysis [A] with the formation of a small cleft (lacunae) progressing to broad acantholytic vesicles and bullae with the characteristic dilapidated brick wall appearance. (Right) Full-thickness epidermal acantholysis in GD may show some dyskeratotic cells [B], but they are different from the degenerating dyskeratotic cells seen in pemphigus. Corps ronds [C] and grains [D] are rarely seen.

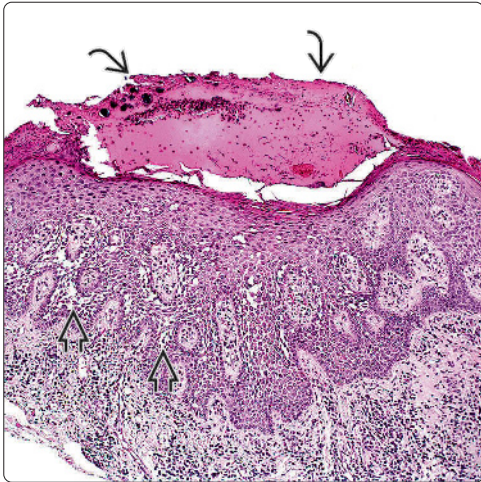


Acantholysis

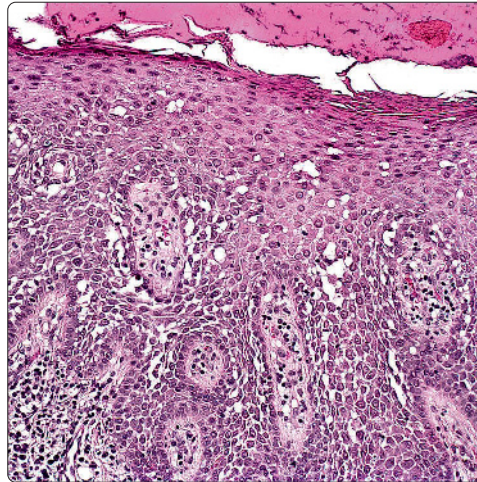




**Spongiotic With Lacunae**

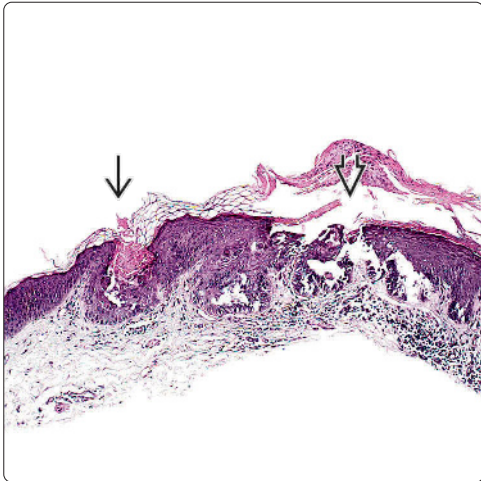


**Spongiotic and Acantholytic**

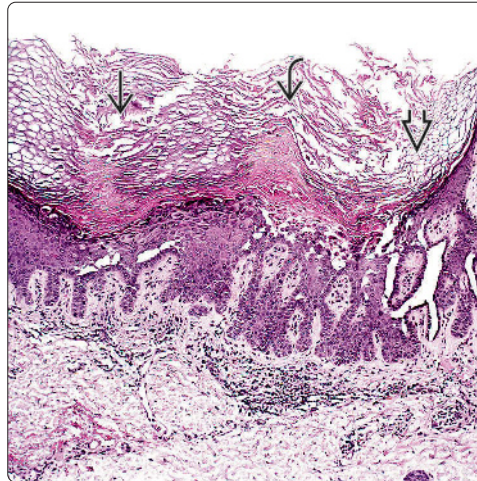


**(Left)** Combined spongiotic and Hailey-Hailey-like patterns show spongiotic foci with lacunae, a partial dilapidated brick wall appearance [X], and a superficial mild to moderate diffuse lymphocytic infiltrate. A crust [X] overlies the spongiotic/acantholytic area. **(Right)** A mixture of spongiotic foci and lacunae in GD gives the characteristic dilapidated brick wall appearance next to the spongiotic changes. Lymphocytes and few eosinophils are seen in the papillary dermis.

**Overlapping Features**

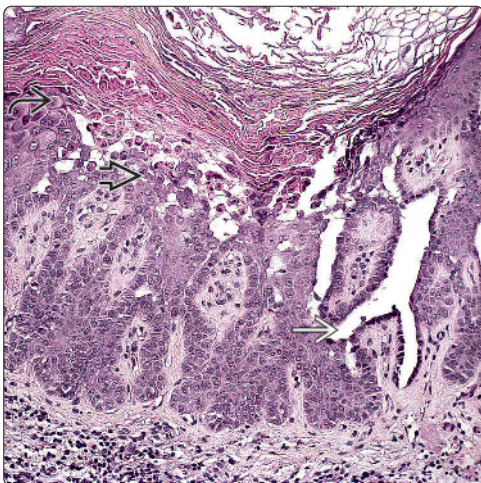


**Overlapping Features**

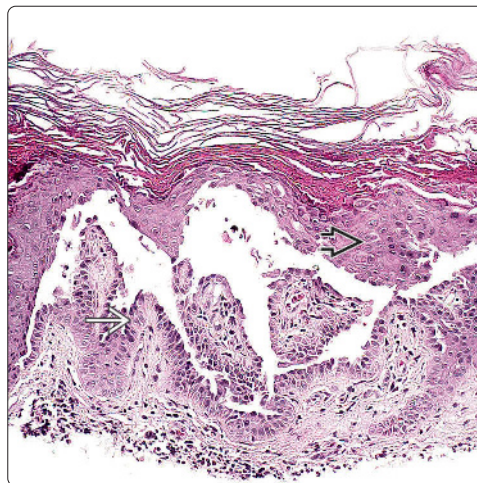


**(Left)** A biopsy specimen tends to demonstrate > 1 histopathological pattern. For example, Darier-like [X] and pemphigus vulgaris-like patterns [X] are both seen in this biopsy specimen. **(Right)** Pemphigus vulgaris-like [X], Darier-like [X], and Hailey-Hailey-like [X] patterns are all seen in this biopsy specimen.

**Overlapping Features of Pemphigus Vulgaris, Dariers, and Hailey-Hailey**



**Overlapping Features of Pemphigus Vulgaris and Hailey-Hailey**



**(Left)** Pemphigus vulgaris-like [X], Darier-like [X], and Hailey-Hailey-like [X] patterns are all seen in this biopsy specimen. **(Right)** Pemphigus vulgaris-like [X] and Hailey-Hailey-like [X] patterns are all seen in this biopsy specimen.



## Darier Disease

## KEY FACTS

**TERMINOLOGY**

- Autosomal dominant genodermatosis characterized by greasy hyperkeratotic papules in seborrheic regions, nail abnormalities, and mucous membrane changes

**ETIOLOGY/PATHOGENESIS**

- Mutations in gene *ATP2A2*

**CLINICAL ISSUES**

- Typical onset in late childhood or adolescence
- Symmetrical, greasy, crusted, keratotic, yellow-brown itchy papules and plaques on seborrheic areas
- Longitudinal nail streaks and nail splitting with V-shaped notch at distal margin
- White papules with cobblestone appearance on buccal mucosa

**MICROSCOPIC**

- Several discrete foci of suprabasal clefts with acantholytic dyskeratotic cells surmounted by vertically orientated parakeratotic columns
- Little, if any, inflammatory cell infiltrate

**TOP DIFFERENTIAL DIAGNOSES**

- Grover disease
- Hailey-Hailey disease
- Acantholytic dermatosis of genitocrural area

**DIAGNOSTIC CHECKLIST**

- Focal acantholytic dyskeratosis that typifies Darier disease (DD) represents histological reaction pattern and is not specific for this condition
- Clinicopathological correlation is essential

Crusted Keratotic Papules of Darier Disease



*This photograph shows typical clinical features of Darier disease (DD), namely greasy, crusted, keratotic, yellow-brown papules and plaques on seborrheic areas.*



## TERMINOLOGY

### Abbreviations

- Darier disease (DD)

### Synonyms

- Darier-White disease; keratosis follicularis

### Definitions

- Autosomal dominant genodermatosis characterized by
  - Clinically
    - Greasy hyperkeratotic papules in seborrheic regions
    - Nail abnormalities
    - Mucous membrane changes
  - Histopathologically
    - Acantholysis
    - Dyskeratosis

## ETIOLOGY/PATHOGENESIS

### Etiology

- Mutations in gene *ATP2A2*
  - Located on 12q24.1
  - Encodes sarcoplasmic/endoplasmic reticulum  $\text{Ca}^{2+}$ -ATP isoform 2 protein (SERCA2)

### Pathophysiology

- SERCA2 maintains low cytoplasmic  $\text{Ca}^{2+}$  level by transporting calcium ions from cytosol into lumen of endoplasmic reticulum
- SERCA2 mutations cause alterations in cytosolic  $\text{Ca}^{2+}$  homeostasis that result in
  - Dyskeratosis due to reduced expression of antiapoptotic proteins Bcl-2, Bcl-x, and BAX
  - Acantholysis due to impaired trafficking of desmoplakin and abnormal desmosomal assembly
  - Formation of immature adhesion complexes between keratinocytes
    - Decreased desmoglein 3, desmocollin 3, desmoplakin, and cadherins, such as E-cadherin
    - These are localized more in perinuclear and endoplasmic reticulum distribution rather than at plasma membrane

### Inciting Factors

- Environmental
  - Heat, humidity, sunlight, UVB exposure, mechanical trauma
- Medications
  - Lithium, oral corticosteroids
- Endogenous
  - Sweating, menstruation

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - 4 new cases per 1 million over 10 years
- Age
  - Typical onset in late childhood or adolescence
- Sex
  - M:F = 1:1

- Ethnicity
  - Worldwide distribution

### Site

- Seborrheic distribution, such as forehead, temples, ears, nasolabial folds, scalp, upper chest, and back
- Flexural areas, including axillae, inframammary fold, groin, and perineum
- Hands and nails
- Mucosal surfaces of mouth, anogenital mucosa, pharynx, larynx, and esophagus

### Presentation

- Symmetrical, greasy, crusted, keratotic, yellow-brown itchy papules and plaques
- Flexural malodorous, hypertrophic, and vegetative plaques
- Acrokeratosis verruciformis-like lesions on dorsum of hands and feet
- Palmar pits
- Localized, linear, and comedonal variants also described
- Longitudinal white &/or red nail streaks; subungual hyperkeratosis; longitudinal nail splitting with V-shaped notch at distal margin
- White papules with cobblestone appearance on mucosa of cheeks, palate, and gums
- Other clinical variants include hypertrophic, vesiculobullous, comedonal, hemorrhagic, linear, or segmental types
- Neuropsychiatric abnormalities including epilepsy, bipolar disorder, and mental retardation have been described in some cases
- May have learning disabilities in small number of affected patients

### Laboratory Tests

- Gene sequencing can be used to identify mutations in *ATP2A2* gene

### Treatment

- Options, risks, complications
  - Increased susceptibility to cutaneous bacterial, fungal, and viral infections (herpes simplex, vaccinia, and poxvirus)
  - Life-threatening Kaposi varicelliform eruption is rare but important complication
- Adjuvant therapy
  - Emollients, hygiene, sunscreen, cool cotton clothing, and avoidance of hot environment
- Drugs
  - Topical treatment includes antiseptics, topical steroid/antibiotic combinations, and retinoids
  - Systemic medications include oral retinoids, oral antibiotics, oral acyclovir, oral contraceptives, diclofenac, and cyclosporine
- Surgical approaches
  - Dermabrasion or laser treatment may prove useful in limited areas

### Prognosis

- Disease persists throughout life in majority of patients

## MICROSCOPIC

### Histologic Features

- Focal acantholytic dyskeratosis that typifies DD represents histological reaction pattern and is not specific for this condition
- Typical lesions of DD show
  - Suprabasal clefts in discrete foci in epidermis
  - Acantholytic, dyskeratotic cells in spinous and granular layers (so-called corps ronds)
  - Acantholytic parakeratotic cells (so-called grains)
  - Thickened epidermis above suprabasal clefts
  - Columns of parakeratosis above acantholytic and dyskeratotic cells
  - Sparse superficial perivascular inflammatory cell infiltrate with lymphocytes

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- **Grover disease (transient acantholytic dermatosis)**
  - May be indistinguishable from DD (Darier type of Grover disease)
  - Findings of pemphigus vulgaris or foliaceus, Hailey-Hailey disease (HHD), spongiosis with acantholysis, and acantholytic dyskeratosis in same biopsy specimen
  - Prominent inflammatory cell infiltrate with eosinophils in addition to lymphocytes
  - Only subtle clefting and acantholysis
- **HHD (familial benign chronic pemphigus)**
  - Suprabasal blisters rather than suprabasal clefts
  - Acantholysis that occurs across broad front (so-called dilapidated brick wall appearance) rather than in discrete foci
  - Polygonal, acantholytic, and progressively dyskeratotic cells throughout at least 1/2 thickness of thickened epidermis
  - Moderately dense infiltrate of inflammatory cells
- **Acantholytic dermatosis of genitocrural area (papular acantholytic dyskeratosis of genitocrural region)**
  - Resembles both HHD and DD (with Hailey-Hailey-like pattern of acantholysis)
  - Clinical presentation is most helpful in distinguishing this process
- **Acantholytic dyskeratotic acanthoma**
  - May be indistinguishable histopathologically from solitary papule of DD but is single isolated lesion
- **Galli-Galli disease**
  - Digitiform hyperpigmented epidermal rete ridges
  - Foci of suprabasal acantholysis and sometimes dyskeratosis
- **Other disorders with acantholysis &/or dyskeratosis**
  - Pemphigus vulgaris
  - Linear epidermal nevus
  - Warty dyskeratoma
  - Focal acantholytic dyskeratosis as incidental finding may be found in variety of lesions, such as basal cell carcinoma, melanocytic nevi, melanoma, etc.

### Clinical

- **Seborrheic dermatitis**

- Similar distribution of lesions
- Waxy, scaly, erythematous papules and plaques
- **Grover disease**
  - Acquired, usually transient, but sometimes persistent disease of unknown etiology
  - No abnormality in *ATP2A2* gene
  - Pruriginous small, discrete, crusted, erythematous papules and papulovesicles
  - Usually on chest, back, and thighs of middle-aged or elderly patients
- **Galli-Galli disease**
  - Acantholytic variant of Dowling-Degos disease
  - Autosomal dominant disorder due to mutation in *KRT5* gene on chromosome 12q13
  - Reddish-brown, hyperkeratotic, scaly, pruritic papules
  - Confluent, reticulated hyperpigmented lesions
  - Involvement of trunk, neck, and both flexor and extensor surfaces of extremities
- **HHD (familial benign chronic pemphigus)**
  - Autosomal dominant genodermatosis
  - Mutations in *ATP2C1* gene on chromosome 3q22.1, which encodes  $\text{Ca}^{2+}$  pump protein
  - Flaccid vesicles and vesiculopustules; erosions; macerated and fissured plaques
  - Predilection for neck and intertriginous areas, such as axillary, genitocrural, perianal, and inframammary regions
- **Acantholytic dermatosis of genitocrural area (papular acantholytic dyskeratosis of genitocrural region)**
  - Variably pruritic, solitary or multiple white papules, solitary nodules, and erythematous or white small plaques present on
    - Vulvocrural areas of young or middle-aged female patients
    - Penis, scrotum, thigh, and perianal region in male patients
  - No similar abnormalities elsewhere
  - No family history of DD or HHD

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Onset in 1st or 2nd decade
- Widespread, rough-surfaced, dirty brown, keratotic papules in seborrheic distribution
- Mucous membranes and nail units usually affected

### Pathologic Interpretation Pearls

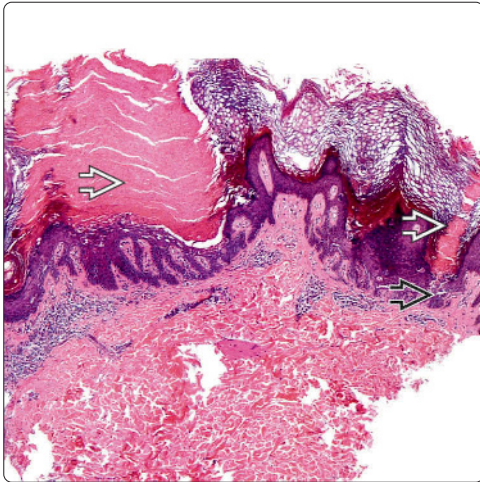
- Focal acantholytic dyskeratosis that typifies DD represents histological reaction pattern and is not specific for this condition
- Several discrete foci of suprabasal clefts with acantholytic dyskeratotic cells surmounted by vertically orientated parakeratotic column

## SELECTED REFERENCES

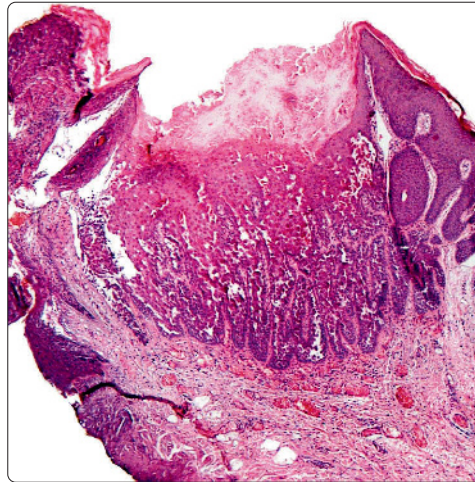
1. Lacarrubba F et al: Darier disease: Dermoscopy, confocal microscopy, and histologic correlations. *J Am Acad Dermatol.* 73(3):e97-9, 2015
2. Dodiuk-Gad R et al: Bacteriological aspects of Darier's disease. *J Eur Acad Dermatol Venereol.* 27(11):1405-9, 2013



**Parakeratotic Columns**

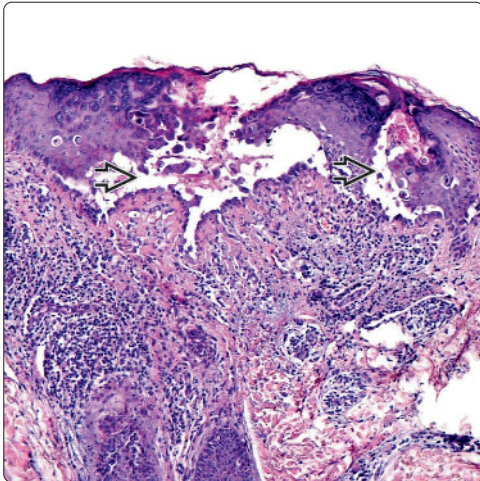


**Acantholytic Dyskeratosis**

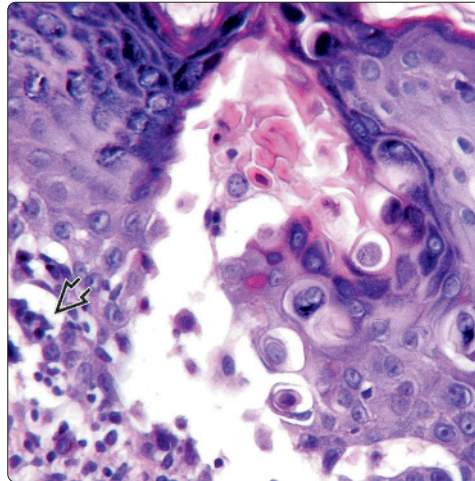


(Left) Biopsy shows several discrete foci of suprabasal clefts with acantholytic dyskeratotic cells surmounted by vertically orientated parakeratotic columns in a typical lesion of DD. (Right) This biopsy comes from a patient with multiple discrete papules in the genitocrural area and shows features of both Hailey-Hailey disease and DD, namely full-thickness acantholysis in a thickened epidermis and prominent dyskeratosis. Similar findings can be seen in papular acantholytic dermatosis of the genitocrural area.

**Focal Acantholytic Dyskeratosis**

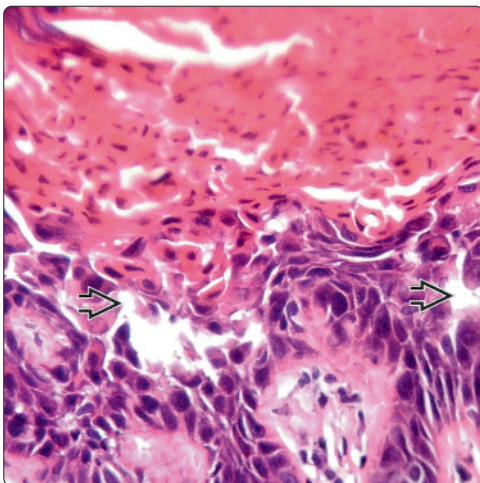


**Spongiosis With Acantholytic Dyskeratosis**

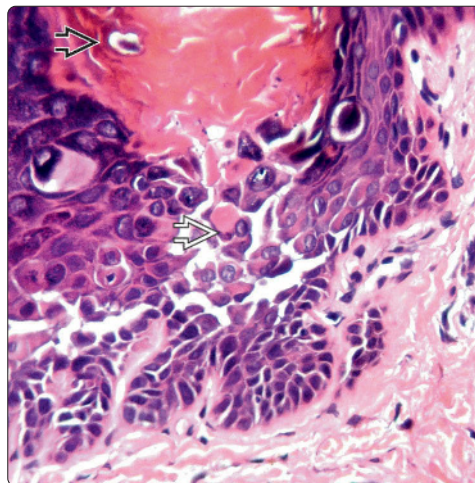


(Left) Focal acantholytic dyskeratosis represents a histological reaction pattern that is not specific for DD, also encountered in Grover disease, as can be seen in this case. Presence of abundant inflammatory cell infiltrate favors Grover disease over DD. (Right) The combination of spongiosis and acantholysis, as can be seen in this close-up view, is a clue for Grover disease. In any event, clinical information should allow for definitive diagnosis.

**Focal Acantholytic Dyskeratosis**



**Corps Ronds and Grains**



(Left) The histological hallmark of DD is focal acantholytic dyskeratosis. (Right) Close-up view reveals acantholytic dyskeratotic cells in spinous and granular layer (so-called corps ronds) and acantholytic parakeratotic cells (so-called grains).



# Porokeratosis

## KEY FACTS

### TERMINOLOGY

- Porokeratosis: Keratinocytic proliferation with clonal keratinocytes resulting in clinically and morphologically distinct keratinization disorder
- Several clinical variants of porokeratosis with overlapping features exist among described varieties

### CLINICAL ISSUES

- **Porokeratosis of Mibelli** manifests as 1 or more asymptomatic large, round to oval, skin-colored to red to brown, annular plaques often occurring unilaterally on extremities
- **Disseminated superficial actinic porokeratosis** has many superficial, coalescent, small, thin, keratotic, skin-colored to red to brown annular plaques or papules with peripheral cornoid lamella occurring bilaterally on sun-exposed extremities
- Porokeratosis has prolonged course, is hard to treat

### MICROSCOPIC

- Cornoid lamella is hallmark feature of all variants and corresponds to clinically evident raised hyperkeratotic peripheral ridge of lesion
- Cornoid lamella is thin, compact column of parakeratosis; granular layer is absent to decreased, and dyskeratotic keratinocytes are present at base

### TOP DIFFERENTIAL DIAGNOSES

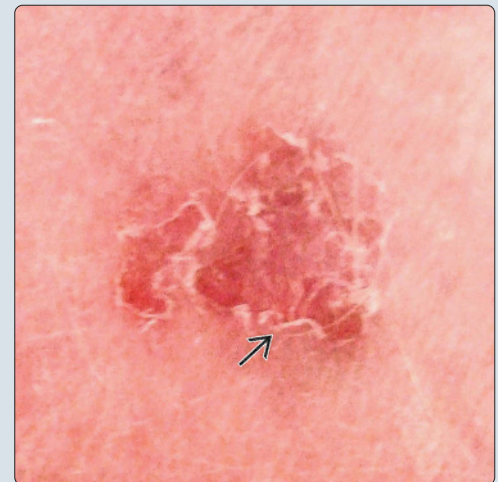
- Cornoid lamellae: Not specific for porokeratosis and can be seen in epidermal nevi as well as normal skin
- Benign lichenoid keratosis
- Clinically linear lesions

### Clinical Presentation of DSAP

(Left) Disseminated superficial actinic porokeratosis (DSAP) presents here as multiple, small, well-demarcated, erythematous, annular plaques with raised hyperkeratotic peripheral ridges (cornoid lamellae). (Right) Porokeratosis of Mibelli demonstrates a sharply demarcated oval plaque with an erythematous center surrounded by a raised, hyperkeratotic, peripheral ridge that represents the cornoid lamella.

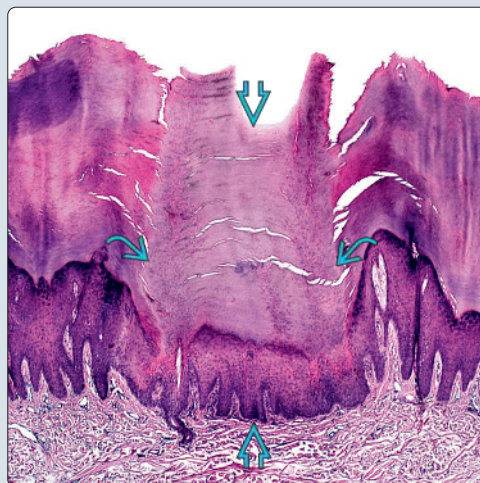


### Cornoid Lamella



### Column of Parakeratosis

(Left) This case of porokeratosis shows 2 closely approximated, poorly staining, compact columns of porokeratosis (cornoid lamellae) that are slightly angulated toward the acanthotic and hyperkeratotic central epidermal area of lesion. (Right) A closer view of one cornoid lamella shows the characteristically absent epidermal granular layer, many dyskeratotic keratinocytes, and vacuolated keratinocytes in the epidermis beneath the parakeratotic column.



### Dyskeratosis and Absent Granular Layer





## TERMINOLOGY

### Abbreviations

- Disseminated superficial actinic porokeratosis (DSAP), disseminated superficial porokeratosis (DSP), porokeratosis palmaris et plantaris disseminata (PPPD), punctate porokeratosis (PP), linear porokeratosis (LP)

### Synonyms

- Inclusive term porokeratosis may be used to refer to any or all of various distinct clinical variants of porokeratosis

### Definitions

- Keratinocytic proliferation resulting in clinically and morphologically distinct keratinization disorder
  - Hyperkeratotic plaques or papules surrounded by centrifugally expansile, thread-like, raised border that results in characteristic cornoid lamella
- Several clinical variants of porokeratosis with overlapping features exist among described varieties
  - Classic variant:** Porokeratosis of Mibelli
  - Common disseminated variants:** DSAP and DSP
  - Rare variants:** PPPD, LP, porokeratosis ptychotropica, PP, CAP syndrome (craniosynostosis, anal anomalies, and porokeratosis), reticulate form, and many others

## ETIOLOGY/PATHOGENESIS

### Developmental Anomaly

- Genetically heterogeneous condition that may be familial and tends to be inherited in autosomal dominant manner
- Fully penetrant by 4th decade of life
- Pathogenetic mechanisms are still somewhat unclear
- Multiple current proposed concepts of pathogenetic mechanisms
  - Loci at chromosome bands 12q23.2-24.1 and 15q25.1-26 (*DSAP1* and *DSAP2*) described in familial disseminated superficial actinic porokeratoses
    - Locus at *DSAP1* corresponds to *SART3*, candidate gene encoding tumor rejection antigen and felt to be involved in regulation of mRNA splicing
    - SART3* mutations may thus result in altered proliferation and transformation of epithelial cells
  - Mutations in mevalonate kinase have been identified in DSAP
  - Centrifugal expansion of cornoid lamellae in lesions may reflect migration of mutant clone of keratinocytes based on DNA ploidy and chromosome abnormalities
  - Higher prevalence of porokeratosis in immunosuppressed patients suggests impaired immunity, which permits disease in genetically predisposed
- CAP syndrome is rare genodermatosis found in only a few ethnically diverse families so far
  - Main phenotypic features are craniosynostosis and clavicular hypoplasia, anal anomalies, and widespread, small, porokeratotic papules affecting face and extremities, starting at 1 month of age

## CLINICAL ISSUES

### Epidemiology

- Incidence

- Relatively common pathological process
  - DSAP is most common clinical variant
- Age
  - Classic porokeratosis of Mibelli and rare LP variant begin during infancy or childhood with expansion of lesions in adulthood
  - DSAP and DSP variants often develop during 3rd or 4th decade of life
  - PPPD and PP variants appear during adolescence and early adulthood
- Sex
  - Porokeratosis of Mibelli and PPPD show male predilection
  - DSAP and DSP both show female predilection: F:M = 3:1

### Site

- Distribution and site of lesions varies depending on clinical variant of porokeratosis
  - Porokeratosis of Mibelli develops as 1 or more round to oval plaques unilaterally on extremities
  - DSAP is typically widely distributed symmetrically over sun-exposed areas of extremities, with rare facial involvement and usual sparing of palms, soles, and mucous membranes
  - DSP occurs symmetrically on extremities similar to DSAP, but sun-protected areas are not spared
  - Porokeratosis ptychotropica involves body folds, namely gluteal and inguinal creases

### Presentation

- Asymptomatic (occasionally pruritic), persistent, annular plaques or papules with characteristic circumferential, raised, hyperkeratotic ridge (rim) at periphery corresponding to cornoid lamella
- Porokeratosis of Mibelli**
  - Manifests as 1 or more asymptomatic, large, round to oval, skin-colored to red to brown, annular plaques often occurring unilaterally on extremities
  - Usually presents in adults as persistent lesions resistant to multiple therapies; some lesions have developed in immunosuppressed patients
  - Lesions initially arise in childhood as small, keratotic papule(s) expanding peripherally over period of years
  - Expanding lesions leave atrophic center surrounded by cornoid lamella consisting of thin, well-demarcated, elevated, guttered, keratotic rim usually  $\geq 1$  mm in height
  - Peripheral expansion of lesions occurs into adulthood with center appearing hyperpigmented, hypopigmented, depressed, or atrophic
- DSAP**
  - Many superficial, coalescent, uniformly small ( $\leq 1$  cm), annular, thin, keratotic, skin-colored to erythematous to brown plaques or papules with peripheral cornoid lamella
  - Lesions are more generalized than other variants, often with > 50 lesions present symmetrically in sun-exposed areas of extremities
  - May rarely coexist with other forms of porokeratosis, including linear and Mibelli variants; may develop in immunosuppressed patients

- Exacerbated by UV light; history of worsening of lesions upon sun exposure usually reported
- **DSP**
  - Lesions morphologically similar to those of DSAP, but no sparing of sun-protected areas
- **LP**
  - Linear erythematous plaques measuring a few cm in size present typically along lines of Blaschko
- Porokeratosis ptychotropica
  - Hyperkeratotic papules and plaques in gluteal and inguinal creases

### Treatment

- Intervention usually unnecessary and disease surveillance preferred since treatment is difficult with variable and poorly standardized treatment outcomes
- Treatment may be pursued if lesions are problematic or cosmetically unacceptable
- Treatment options include potent topical steroids, keratolytics, topical/oral retinoids, 5-fluorouracil, imiquimod, calcipotriol, cryotherapy, carbon dioxide or pulsed dye lasers, excision, electrocautery, others

### Prognosis

- Prolonged course; often difficult to treat
  - Chronic, slowly progressive, and relatively asymptomatic with lesions increasing in size and number over time
  - Treatment usually unnecessary; disease surveillance is standard since lesions persist indefinitely without treatment
- Generally regarded as benign lesions, but malignant transformation can occur
  - Increased size and duration of lesions of porokeratosis increase risk of malignancy
  - Increased risk of development of malignancy (squamous cell carcinoma, Bowen disease, basal cell carcinoma) in up to 11% of those affected
    - Squamous cell carcinoma, invasive or in situ, is most common associated malignancy
  - Giant porokeratoses, LP, and immunosuppression-associated variants seem more prone to malignant change than other variants
    - Closer surveillance and lower threshold for biopsy of suspicious lesions appropriate in these cases

### MACROSCOPIC

#### General Features

- Numerous or solitary, annular, round to oval (rarely linear), red to brown papules or plaques
- Atrophic to hyperkeratotic lesions that range from few mm to many cm in size depending on clinical setting

### MICROSCOPIC

#### Histologic Features

- Characteristic histopathologic features are similar among various clinical variants
  - Cornoid lamella is hallmark feature of porokeratosis and corresponds to clinically evident, raised hyperkeratotic peripheral rim of lesion

- Cornoid lamella is angulated, thin, compact column of parakeratosis overlying area of epidermal dysmaturation; granular layer is decreased to absent, and dyskeratotic cells are present at base
  - Cornoid lamellae are usually angulated so inferior aspect points away from center of lesion and parakeratotic tip is angulated toward center
  - DSAP often shows 2 cornoid lamellae (1 on each side of hyperkeratotic plug), lichenoid inflammatory reaction, and dermal solar elastosis
  - Mibelli variant shows epidermal invagination at site of cornoid lamella; multiple cornoid lamellae are seen in linear and reticulate variants
  - Basal vacuolar changes and epidermal vacuolization beneath cornoid lamella as well as superficial dermal perivascular chronic inflammation may be seen
  - Biopsy must include raised, advancing peripheral rim of lesion to show cornoid lamella
  - Cornoid lamella is very characteristic of porokeratosis, but not pathognomonic
  - Porokeratosis ptychotropica has multiple columnar cornoid lamellae
- Epidermis in center of lesions may appear normal or show atrophy, hyperkeratosis, or lichenoid reaction

### Cytologic Features

- Keratinocytic dysplasia ranging from mild atypia to in situ or invasive squamous cell carcinoma rarely occurs

### DIFFERENTIAL DIAGNOSIS

#### Other Lesions With Cornoid Lamellae

- Cornoid lamellae are not specific for porokeratosis and can occasionally be seen as minor reaction pattern in epidermal nevi, verruca, and normal skin
- Lesions of porokeratosis are most often clinically distinctive and diagnosis is usually clinically apparent, but atypical lesions may require biopsy

#### Benign Lichenoid Keratosis

- Lichenoid inflammatory reaction pattern is seen in porokeratosis, so presence of cornoid lamella must be excluded before rendering diagnosis

#### Clinically Linear Lesions

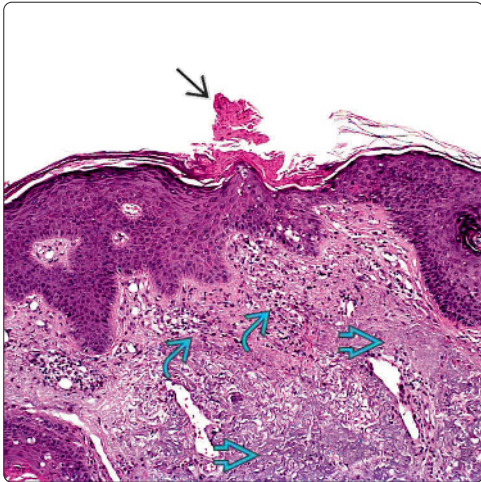
- Linear inflammatory verrucous epidermal nevus, incontinentia pigmenti, lichen planus, and others do not usually demonstrate cornoid lamellae

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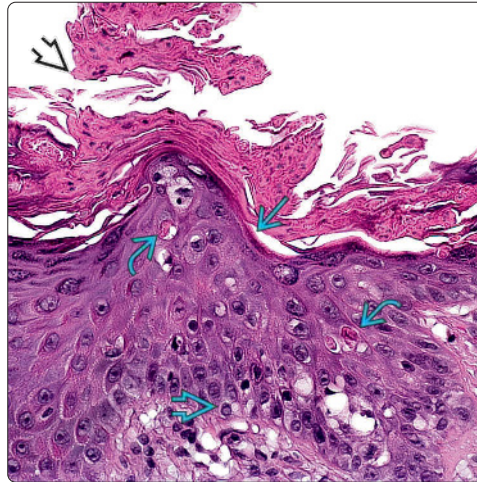
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DSAP



Cornoid Lamella of DSAP

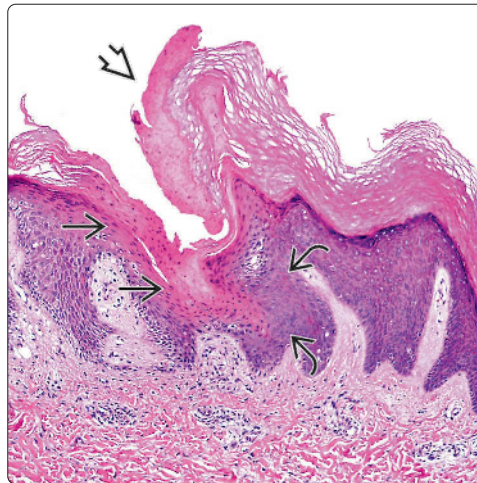


(Left) DSAP shows a slightly angulated compact column of parakeratosis (cornoid lamella) with solar elastosis and patchy, mild, superficial dermal chronic inflammation in underlying dermis. (Right) A higher power view of this example of DSAP reveals a thinned to focally absent epidermal granular layer with scattered dyskeratotic epidermal keratinocytes and basal vacuolar changes beneath a cornoid lamella.

Angulated Cornoid Lamella

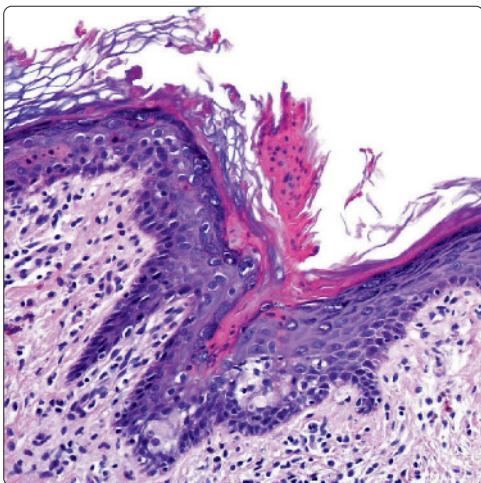


Cornoid Lamella

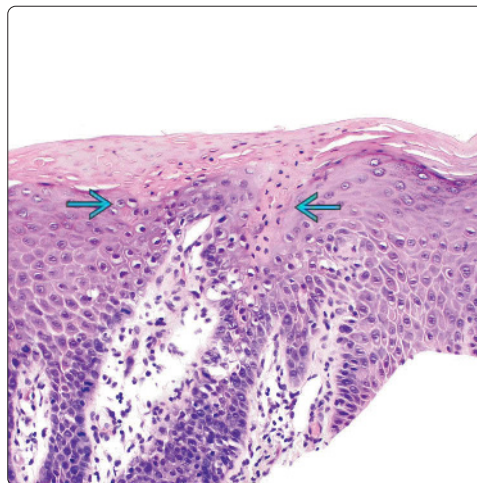


(Left) Porokeratosis demonstrates a cornoid lamella angulated toward the mildly acanthotic central area of the lesion. There is underlying superficial chronic perivascular inflammation. (Right) An angulated compact column of parakeratosis (cornoid lamella) arises from the underlying epidermis. Beneath the cornoid lamella, the epidermal granular cell layer is absent and scattered dyskeratotic cells are present at the base.

Column of Parakeratosis



Porokeratosis Ptychotropica



(Left) A discrete column of parakeratosis overlies a zone of hypogranulosis and dyskeratosis, defining the cornoid lamella. (Right) Two cornoid lamellae are seen adjacent to one another in this example of porokeratosis ptychotropica.



## Ichthyosis

## KEY FACTS

## TERMINOLOGY

- Ichthyosis vulgaris (IV)
  - a.k.a. ichthyosis simplex
- Lamellar ichthyosis (LI)
  - a.k.a. nonbullous congenital ichthyosiform erythroderma
- X-linked ichthyosis (XLI): Steroid sulfatase deficiency
  - a.k.a. X-linked ichthyosis

## ETIOLOGY/PATHOGENESIS

- IV: Common autosomal dominant defect causing profilaggrin deficiency
- XLI: X-linked recessive condition resulting in steroid sulfatase deficiency (aryl sulfatase C)
- LI: Autosomal recessive (mostly) condition resulting in decreased transglutaminase-1 activity

## CLINICAL ISSUES



- Thick, dark scales on skin
- Sites involved and prognosis varies with subtype

- IV and XLI are related to prolonged retention of stratum corneum (retention hyperkeratoses)
  - IV: Most common type, begins in childhood
    - Acquired variant occurs in patients with medication, malignancy, connective tissue disease, and sarcoidosis
  - XLI: Almost always in males, rare in females
    - Prolonged labor: Delivered via cesarean section (deficient placental sulfatase)
- LI is due to hyperproliferation of epidermis
  - Uncommon
    - Collodion membrane at birth

## MICROSCOPIC

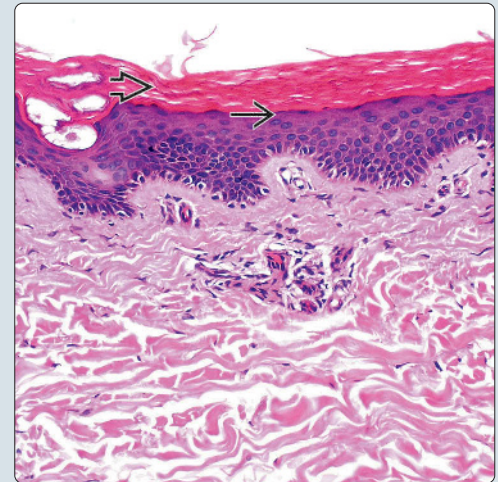
- IV: Compact eosinophilic orthokeratosis
  - Decreased or absent granular layer
  - Decreased filaggrin production
- XLI: Marked hyperkeratosis with normal granular cell layer
- LI: Marked compact hyperkeratosis with normal granular layer

## Fish-Like Plates in Ichthyosis Vulgaris




(Left) *Ichthyosis vulgaris* presents as fish-like plates of dry symmetric skin over the shoulder of this patient who has had it all of her life. (Right) *Ichthyosis vulgaris* is the most common subtype and demonstrates compact eosinophilic orthokeratosis  and a decreased or absent granular layer . (Courtesy S. Billings, MD.)



## Compact Eosinophilic Orthokeratosis in Ichthyosis Vulgaris

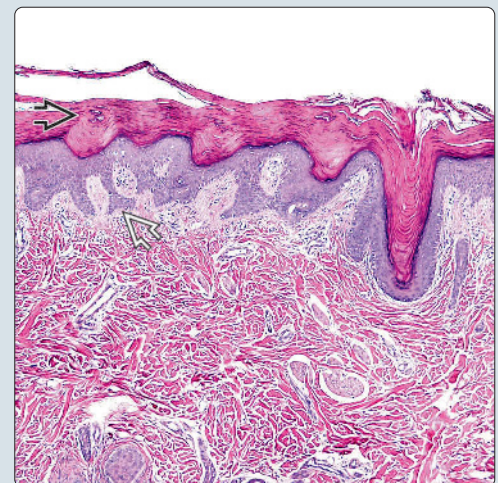


## Quadrilateral Scale in Lamellar Ichthyosis

(Left) *Lamellar ichthyosis* presents as a plate-like quadrilateral scale  over the extensor surface of the arm in this patient. (Right) This example of lamellar ichthyosis shows very thick, compact orthokeratosis  in the stratum corneum along with some mild acanthosis .



## Thick, Compact Orthokeratosis in Lamellar Ichthyosis





## TERMINOLOGY

### Abbreviations

- Numerous variants
  - Ichthyosis vulgaris (IV)
  - X-linked ichthyosis (XLI)
  - Lamellar ichthyosis (LI)

### Synonyms

- IV: Ichthyosis simplex
- XLI: Steroid sulfatase deficiency
- LI: Nonbullous congenital ichthyosiform erythroderma

### Definitions

- Group of heterogeneous disorders causing abnormal cornification (scale) of epidermis
- Greek word ichthys means fish

## ETIOLOGY/PATHOGENESIS

### Developmental Anomaly

- IV: Common autosomal dominant defect causing profilaggrin deficiency
- XLI: X-linked recessive condition resulting in steroid sulfatase deficiency (aryl sulfatase C)
- LI: Autosomal recessive (mostly) condition resulting in decreased transglutaminase-1 activity

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - IV: Most common type, begins in childhood
    - Acquired variant occurs in patients with malignancy, connective tissue disease, and sarcoidosis
    - Also may be associated with certain medications
  - XLI: Almost always in males, rare in females
    - Prolonged labor: Delivered via cesarean section (deficient placental sulfatase)
    - Onset before 3 months of age
  - LI: Uncommon
    - Collodion membrane at birth

### Presentation

- IV: Coarse brown scales predominantly on extensor surfaces of extremities
  - Spares intertriginous areas
  - Accentuated skin markings and hyperkeratosis on palms (keratosis punctata)
  - May have associated atopic dermatitis &/or keratosis pilaris
- XLI: Dark brown scales on posterior neck (dirty neck), extremities, and trunk
  - Spares face, scalp, elbows, palms, and soles
  - Corneal opacities of posterior capsule (Descemet membrane)
  - Cryptorchidism: Increased risk of testicular cancer
- LI: Large, plate-like (armor), brown quadrilateral scales with underlying erythema
  - Adherent in middle with free edges on side
  - Hyperkeratosis of palms and soles
  - Nail dystrophy, scarring alopecia, hypernatremia

- Hypohidrosis (increased risk of heat stroke)
- Ectropion and eclabium

### Treatment

- Topical treatments consist of various emollients, keratolytics, and retinoids

### Prognosis

- IV: Improves with time and warm, moist environments
- XLI: Waxes and wanes throughout life; worsens with age
  - May clear completely during hot, moist summers
- LI: Lifelong condition

## MICROSCOPIC

### Histologic Features

- IV: Compact eosinophilic orthokeratosis
  - Decreased or absent granular layer
  - Decreased filaggrin production
- XLI: Marked hyperkeratosis with normal granular cell layer
- LI: Marked compact hyperkeratosis with normal granular layer

## ANCILLARY TESTS

### Electron Microscopy

- IV: Small crumbled granules in granular layer due to defective keratohyaline synthesis

### Slit-Lamp Examination

- XLI: Corneal opacities of posterior capsule (Descemet membrane)

### Serum Electrophoresis

- XLI: Lipoprotein electrophoresis shows increased cholesterol sulfate

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Eczema
  - Spongiosis
  - Superficial, perivascular, predominantly lymphocytic infiltrate
- Epidermolytic acanthoma
  - Solitary, wart-like lesion
  - Hyperkeratosis with acanthosis
  - Hypergranulosis, epidermolysis
- Hyperkeratosis palmaris et plantaris (palmoplantar keratoderma)
  - Hyperkeratosis with spongy appearance
  - Dilatation of eccrine ducts

### Clinical

- Acquired ichthyosis
  - Secondary to malignancy, bone marrow transplant, or medications

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## KEY FACTS

### TERMINOLOGY

- Taken strictly, epidermolytic hyperkeratosis (EHK) is just histologic finding and not diagnostic entity
- However, traditionally, EHK is defined as diagnostic entity consisting of skin fragility with development of erythema, blisters, and crusted plaques due to mutation in keratin 1 (*KRT1*) and 10 (*KRT10*) genes

### ETIOLOGY/PATHOGENESIS

- Inherited (keratin 1 and keratin 10 gene mutation), acquired, or incidental
- Autosomal dominant inheritance due to mutations in *KRT1* and *KRT10* genes
- Acquired due to sporadic *KRT1* and *KRT10* mutations in up to 50% of cases

### CLINICAL ISSUES

- Lifelong, but tends to improve with age
- Erythema, crusted plaques, and blisters since birth

- Blistering improves with age
- Around 3-4 years of age, crusty plaques develop in flexures
- Palmoplantar hyperkeratosis
- Frequent infections of crusty plaques because it is hard to keep affected skin clean
- No effective treatment exists

### MICROSCOPIC

- Orthohyperkeratosis with irregular purple clumps and vacuoles in upper 1/2 of epidermis
- Compact orthohyperkeratosis, sometimes with papillomatosis
- Prominent granular layer with large, irregularly shaped keratohyaline granules
- Vacuolar appearance of granular and spinous layers due to disruption of keratinocytes, i.e., epidermolysis with development of vesicles

Crusted Plaques in Creases

(Left) Epidermolytic hyperkeratosis (EHK) presents as erythematous, scaly, crusted plaques. (Courtesy J. Conlon, MD.) (Right) EHK clinically shows erythematous, scaly plaques, which may present anywhere on the body but predominate around creases and folds (intertriginous areas).

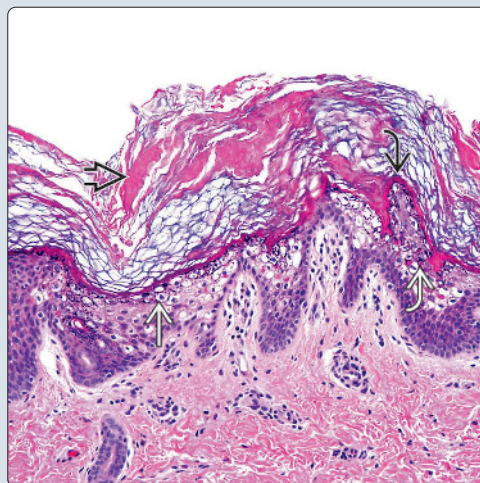


Crusted Plaques

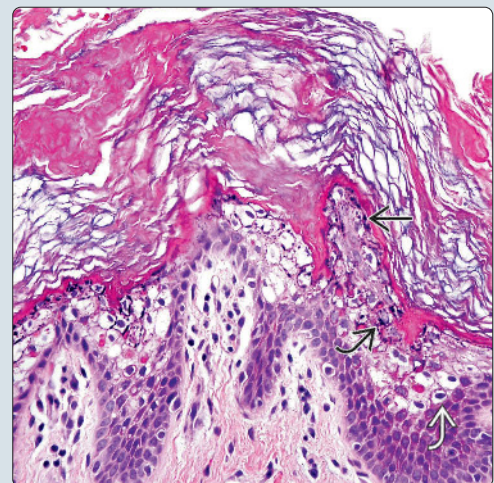


Orthohyperkeratosis and Papillomatosis

(Left) EHK demonstrates orthohyperkeratosis and subtle papillomatosis. There are purple irregular clumps and vacuolar changes in the upper epidermis. (Right) EHK shows vacuolar degeneration of keratinocytes with purple clumps composed of keratin and keratohyaline granules. Note the bright purple perinuclear clumping composed of retracted keratin.



Large Irregular Granules





## TERMINOLOGY

### Abbreviations

- Epidermolytic hyperkeratosis (EHK)

### Synonyms

- Bullous ichthyosis, bullous ichthyosiform erythroderma, bullous congenital ichthyosiform erythroderma, bullous erythroderma ichthyosiformis congenita of Brocq

### Definitions

- Taken strictly, EHK is just histologic finding and not diagnostic entity
  - However, traditionally, EHK is defined as diagnostic entity consisting of skin fragility with development of erythema, blisters, and crusted plaques due to mutation in keratin 1 (*KRT1*) and 10 (*KRT10*) genes

## ETIOLOGY/PATHOGENESIS

### Gene Mutations

- Autosomal dominant inheritance due to mutations in *KRT1* and *KRT10* genes
- Acquired due to sporadic *KRT1* and *KRT10* mutations in up to 50% of cases
- In many cases, presents as incidental histologic finding (focal epidermolytic hyperkeratosis)

## CLINICAL ISSUES

### Presentation

- Erythema, crusted plaques, and blisters since birth
- Blistering improves with age
- Around 3-4 years of age, crusty plaques develop in flexures
- Palmoplantar hyperkeratosis
- Frequent infections of crusty plaques because it is hard to keep affected skin clean
- No specific clinical findings in incidental focal epidermolytic hyperkeratosis

### Treatment

- No effective treatment exists
  - Topical and systemic retinoids have been tried with variable success
  - Topical keratinolytics, systemic or topical antibiotics for secondary infections, and genetic counseling may be helpful

### Prognosis

- Lifelong condition
- Tends to improve with age

## MACROSCOPIC

### General Features

- Crusted plaques and blisters

## MICROSCOPIC

### Histologic Features

- Compact orthohyperkeratosis, sometimes with papillomatosis
- Prominent granular layer with large, irregularly shaped keratohyaline granules

- Vacuolar appearance of granular and spinous layers due to disruption of keratinocytes, i.e., "epidermolysis" with development of vesicles
- Compared with acantholysis, preservation of desmosomes in epidermolysis

## ANCILLARY TESTS

### Electron Microscopy

- Perinuclear clumping of keratin in affected keratinocytes

## DIFFERENTIAL DIAGNOSIS

### Histopathological

- Epidermolytic acanthoma
  - Histologically identical to EHK
  - In contrast to EHK, presents as solitary verrucous lesion
- Palmoplantar keratoderma
  - Very thick skin involving plantar and palmar surfaces of hands and feet
    - Also involves flexor fingers and toes
  - No plaques in flexors like EHK (just involves hands and feet)
  - Characteristic clinical presentation
    - Rarely biopsied

### Clinical

- Ichthyosis hystrix
  - Clinical variant of EHK due to mutation in *KRT1* gene
- Ichthyosis bullosa of Siemens
  - Histologically similar to EHK
  - Mutation in keratin 2e (*KRT2*) gene
  - Limited to flexural areas; no erythroderma
- Palmoplantar keratoderma
  - May have histological features of EHK

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Vacuolar degeneration of keratinocytes with formation of vesicles
- Look for signs of secondary bacterial, viral, or fungal infection, and comment on it to help clinician in management decisions

### Pathologic Interpretation Pearls

- Orthohyperkeratosis with irregular purple clumps (clumped keratin and keratohyaline granules) and vacuoles in upper 1/2 of epidermis
- EHK can occur as focal incidental phenomenon in many skin conditions; therefore, clinical information is essential for accurate diagnosis
  - Actinic keratoses, squamous cell carcinomas, dysplastic nevi, seborrheic keratoses, epidermal cysts, trichilemmal cysts, epidermal nevi, etc. can all show focal EHK

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2. Noursbeck J et al: Semidominant inheritance in epidermolytic ichthyosis. *J Invest Dermatol*. 133(11):2626-8, 2013

## KEY FACTS

### TERMINOLOGY

- Previously referred to as axillary granular parakeratosis
- Defined as abnormal retention of keratohyaline granules in stratum corneum

### CLINICAL ISSUES

- Erythematous to brown papules that coalesce into plaques with variable scale, hyperkeratosis
- Most commonly affects axillae
- May affect other sites
- Female predominance

### MICROSCOPIC

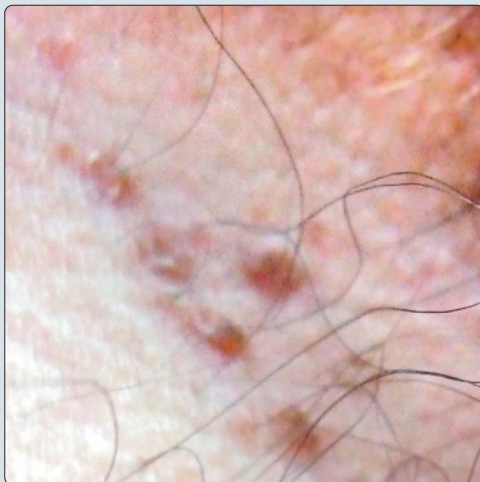
- Stratum corneum appears blue
  - Secondary to parakeratosis
  - Secondary to retained keratohyaline granules

### TOP DIFFERENTIAL DIAGNOSES

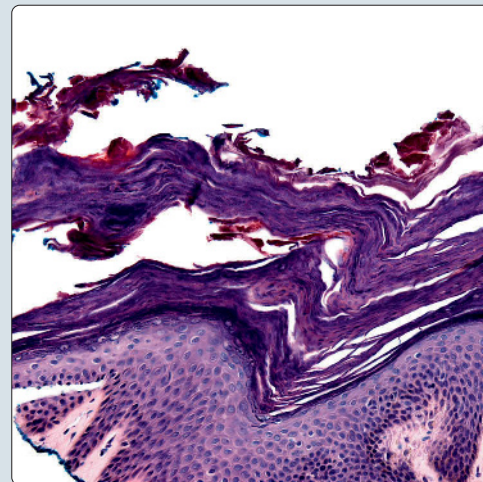
- Incidental granular parakeratosis (incidental histopathologic finding)
  - Seen in association with other clinical lesions
- Granular parakeratotic acanthoma
  - Clinical: Solitary lesion
  - Identical histopathology to granular parakeratosis
- Dermatophyte infection
  - Fungal hyphae [PAS(+)] may be sandwiched between parakeratosis and hyperkeratosis (sandwich sign)

**Granular Parakeratosis Papules in Axilla**

*(Left) Papules of granular parakeratosis in the axilla are pictured here. The papules are tan to light pink with slight hyperkeratosis. (Right) In granular parakeratosis, the stratum corneum appears blue secondary to parakeratosis and retained keratohyaline granules.*

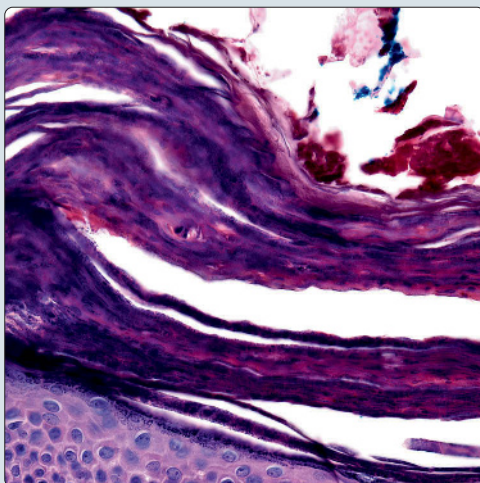


**Blue Stratum Corneum**

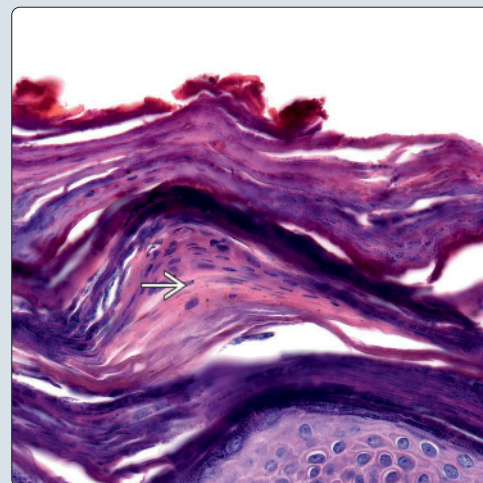


**Parakeratotic Scale**

*(Left) In granular parakeratosis, there is retention of keratohyaline granules in the stratum corneum, which is generally parakeratotic. (Right) In this view of granular parakeratosis, there is a focal area of parakeratosis without retained keratohyaline granules. This area appears more pink in overall color.*



**Keratohyaline Granules Give Blue Color**





## TERMINOLOGY

### Synonyms

- Axillary granular parakeratosis

### Definitions

- Abnormal retention of keratohyaline granules in stratum corneum

## ETIOLOGY/PATHOGENESIS

### Unknown

- Theories: Some postulate that granular parakeratosis is
  - Secondary to irritation induced by deodorant
    - Does not explain cases outside of axillae
  - Related to defective processing of profilaggrin to filaggrin

## CLINICAL ISSUES

### Epidemiology

- Age
  - Generally seen in adults but has been reported in children; rarely congenital
- Sex
  - F > M

### Site

- Most commonly affects axillae but can also affect groin or inframammary regions

### Presentation

- Bilateral or unilateral, and may affect more than 1 intertriginous site
- Erythematous to brown papules that coalesce into plaques with variable scale, hyperkeratosis
- May be pruritic
- Rarely papillomatous or acanthosis nigricans-like

### Prognosis

- May clear spontaneously

## MICROSCOPIC

### Histologic Features

- Stratum corneum appears blue
  - Secondary to retained keratohyaline granules
  - Also secondary to parakeratosis (retained nuclei in stratum corneum)
- Parakeratosis
  - Often confluent
  - May alternate with orthokeratosis
  - Often involves follicular infundibulae
- Generally normal granular layer
- Epidermis
  - Atrophic, acanthotic, or of normal thickness

## DIFFERENTIAL DIAGNOSIS

### Incidental Granular Parakeratosis (Incidental Histopathologic Finding)

- Seen in association with other clinical lesions
  - Molluscum contagiosum

- Dermatomyositis
- Carcinomas

### Granular Parakeratotic Acanthoma

- Clinical: Solitary lesion
- Identical histopathology to granular parakeratosis

### Dermatophyte Infection

- Clinical
  - Erythema with scale
  - May have annular configuration
  - May affect intertriginous sites
- Histopathologic
  - Parakeratosis often present; neutrophils often in stratum corneum
    - Fungal hyphae [PAS(+)] may be sandwiched between parakeratosis and hyperkeratosis (sandwich sign)

### Spongiotic/Eczematous Dermatitis

- Clinical
  - Erythema with scale
  - May affect intertriginous sites
- Histopathologic
  - Parakeratosis often present
    - Serum may be present in parakeratotic crust
  - Epidermis generally spongiotic, often acanthotic

### Psoriasiform Dermatitis

- Clinical
  - Erythema with scale
  - May affect intertriginous sites
- Histopathologic
  - Confluent parakeratosis often present
  - Neutrophils may be present in parakeratosis
  - Epidermis generally acanthotic
  - Often hypogranulosis

### Candidal Infection

- Clinical
  - Erythema with scale
  - May see satellite pustules
  - May affect intertriginous sites
- Histopathologic
  - Neutrophils often in stratum corneum; PAS(+) spores

### Erythrasma

- Clinical
  - Red-brown to pink erythema with scale
  - May affect intertriginous sites
  - Positive coral red fluorescence with Wood lamp
- Histopathologic
  - Filamentous bacteria [PAS(+), gram(+)] in stratum corneum

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2. Ding CY et al: Granular parakeratosis: a comprehensive review and a critical reappraisal. *Am J Clin Dermatol.* 16(6):495-500, 2015
3. Channul J et al: Axillary granular parakeratosis. *Cutis.* 92(2):61, 65-6, 2013

## KEY FACTS

### TERMINOLOGY

- Ectodermal dysplasia that may affect skin, hair, and teeth, as well as internal organs
- Skin findings early in infancy are characteristic, with vesicles/bullae in Blaschkoid streaks

### ETIOLOGY/PATHOGENESIS

- Mosaic disorder, X-linked dominant inheritance
- Defect in *IKBKG* (NEMO) gene that encodes NF- $\kappa$ B essential modulator

### CLINICAL ISSUES

- Vesicular stage (stage 1)
  - Erythematous papules
  - Especially on trunk and extremities
- Verrucous stage (stage 2)
  - Hyperkeratotic, verrucous papules
  - Especially on extremities
- Hyperpigmented stage (stage 3)

- Brown to gray linear lesions that follow Blaschko lines; borders may be scalloped
- Hypopigmented stage (stage 4)
  - Linear, atrophic appearance to skin (may be due to loss of hair follicles)
  - Especially on extremities (calves)

### MICROSCOPIC

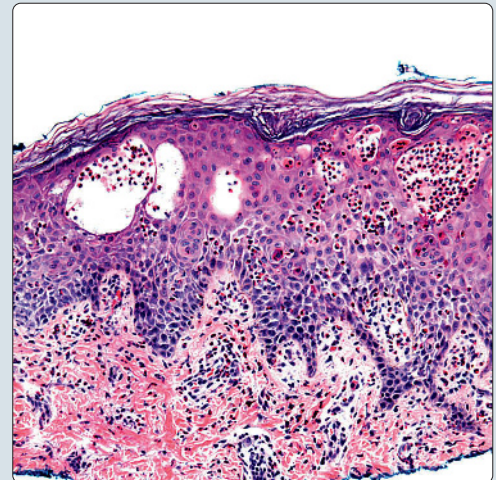
- Vesicular stage (stage 1)
  - Spongiosis &/or vesicles in epidermis with eosinophils and scattered dyskeratotic keratinocytes
- Verrucous stage (stage 2)
  - Epidermal hyperplasia with scattered single or aggregate dyskeratotic keratinocytes
- Hyperpigmented stage (stage 3)
  - Pigment incontinence in papillary dermis
- Hypopigmented stage (stage 4)
  - Atrophic epidermis
  - Reduced number of adnexal structures

**Curved, Linear, Light Brown Streaks**

(Left) This infant has the hyperpigmented stage of incontinentia pigmenti (stage 3), with curved, linear, light brown streaks on the left trunk. (Courtesy D. Mraz Robinson, MD.) (Right) The vesicular stage of incontinentia pigmenti has vesicles in the epidermis with eosinophilic abscesses.

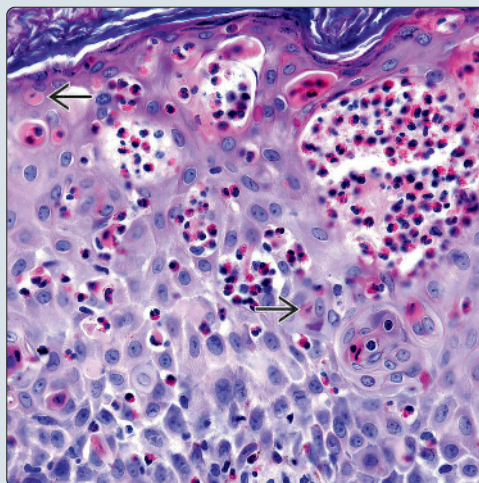


**Vesicle With Eosinophilic Abscesses**

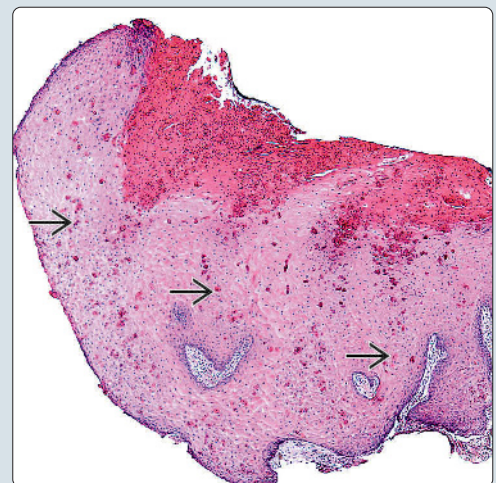


**Apoptotic Keratinocytes With Eosinophilic Spongiosis**

(Left) The vesicular stage (stage 1) of incontinentia pigmenti shows apoptotic keratinocytes in a background of eosinophilic spongiosis (intercellular edema, eosinophils, and eosinophilic abscesses). (Right) The subungual tumors of incontinentia pigmenti have features virtually identical to subungual keratoacanthoma. Hyperkeratosis overlies epithelial hyperplasia and numerous apoptotic keratinocytes.



**Epithelial Hyperplasia of Subungual Tumors**





## TERMINOLOGY

### Abbreviations

- Incontinentia pigmenti (IP)

### Synonyms

- Bloch-Sulzberger syndrome

### Definitions

- Genodermatosis
- Ectodermal dysplasia that may affect skin, hair, and teeth, as well as internal organs
- Skin findings early in infancy are characteristic, with vesicles/bullae in Blaschkoid streaks

## ETIOLOGY/PATHOGENESIS

### Genetics

- Mosaic disorder, X-linked dominant inheritance
- Defect in *IKBKG* (NEMO) gene that encodes NF- $\kappa$ B essential modulator that prevents TNF- $\alpha$ -induced apoptosis

## CLINICAL ISSUES

### Epidemiology

- Age
  - Vesicular stage (stage 1)
    - Typically birth to 2-3 weeks
  - Verrucous stage (stage 2)
    - Typically 2-6 weeks
  - Hyperpigmented stage (stage 3)
    - Typically 2-6 months
  - Hypopigmented stage (stage 4)
    - Typically puberty or later
- Sex
  - Generally lethal in males

### Presentation

- Vesicular stage (stage 1)
  - Erythematous papules
  - Vesicles, rare bullae, pustules
  - Especially on trunk and extremities
- Verrucous stage (stage 2)
  - Hyperkeratotic, verrucous papules
  - Especially on extremities
- Hyperpigmented stage (stage 3)
  - Brown to gray linear lesions that follow Blaschko lines; borders may be scalloped
- Hypopigmented stage (stage 4)
  - Linear, atrophic appearance to skin (may be due to loss of hair follicles)
  - Skin appears hypopigmented
  - Especially on extremities (calves)
- Scarring alopecia on vertex of crown may be present
- Eyebrows/eyelashes may be sparse
- Nails
  - May show pitting, onycholysis, &/or hyperkeratosis
  - Subungual tumors may develop, which can be destructive and erode bone
- Teeth
  - May be peg-shaped or conical
  - May be otherwise malformed, absent, or erupt late

### Laboratory Tests

- Peripheral eosinophilia or leukocytosis may be present in infancy

### Natural History

- Stages may overlap
- Occasionally, any given stage may have longer duration than is typical
- Not all individuals express each stage

### Treatment

- Not necessary for skin changes
- Ophthalmologic evaluation recommended with other consults (e.g., dental, neurologic) as necessary

### Prognosis

- Ocular involvement can cause severe complications, including blindness
- Central nervous system (e.g., seizures, spasticity, developmental delay) &/or skeleton may be involved

## MICROSCOPIC

### Histologic Features

- Vesicular stage (stage 1)
  - Spongiosis &/or spongiotic vesicles in epidermis
  - Scattered apoptotic keratinocytes
  - Eosinophils singly and in clusters in epidermis
- Verrucous stage (stage 2)
  - Epidermal hyperplasia
  - Scattered apoptotic keratinocytes, or whorls of aggregate apoptotic keratinocytes
- Hyperpigmented stage (stage 3)
  - Prominent papillary dermal pigment incontinence
- Hypopigmented stage (stage 4)
  - Atrophic epidermis
  - May see papillary dermal globules of elastin
  - Reduced number of adnexal structures (e.g., hair follicles)
- Subungual tumors
  - Epidermal hyperplasia with numerous apoptotic keratinocytes

## DIFFERENTIAL DIAGNOSIS

### Eosinophilic Spongiosis of Other Blistering Disorders

- Histopathologically typically lack dyskeratotic cells

### Linear and Whorled Nevoid Hypermelanosis (for Stage 3)

- Borders of streaks reticulated clinically without scalloping
- Histopathologically lacks dyskeratosis and eosinophil-rich infiltrate

### Postinflammatory Hyperpigmentation (for Stage 3)

- Clinically is typically not in Blaschkoid distribution
- Histopathologically is identical in appearance to stage 3 IP with pigment incontinence

## SELECTED REFERENCES

1. Minić S et al: Incontinentia pigmenti diagnostic criteria update. Clin Genet. 85(6):536-42, 2014

## Keratosis Pilaris

## KEY FACTS

**ETIOLOGY/PATHOGENESIS**

- Extremely common
- Usually seen in isolation but can be part of rare group of genodermatoses [keratosis pilaris (KP) atrophicans]

**CLINICAL ISSUES**

- Erythematous follicular papules with spiny feeling
- Onset in childhood
- Lesions occur most commonly on extensor surface of upper arms
- May see involvement of thighs or cheeks
- Tends to be persistent but diminishes with age
- Treat with keratolytics or topical retinoids

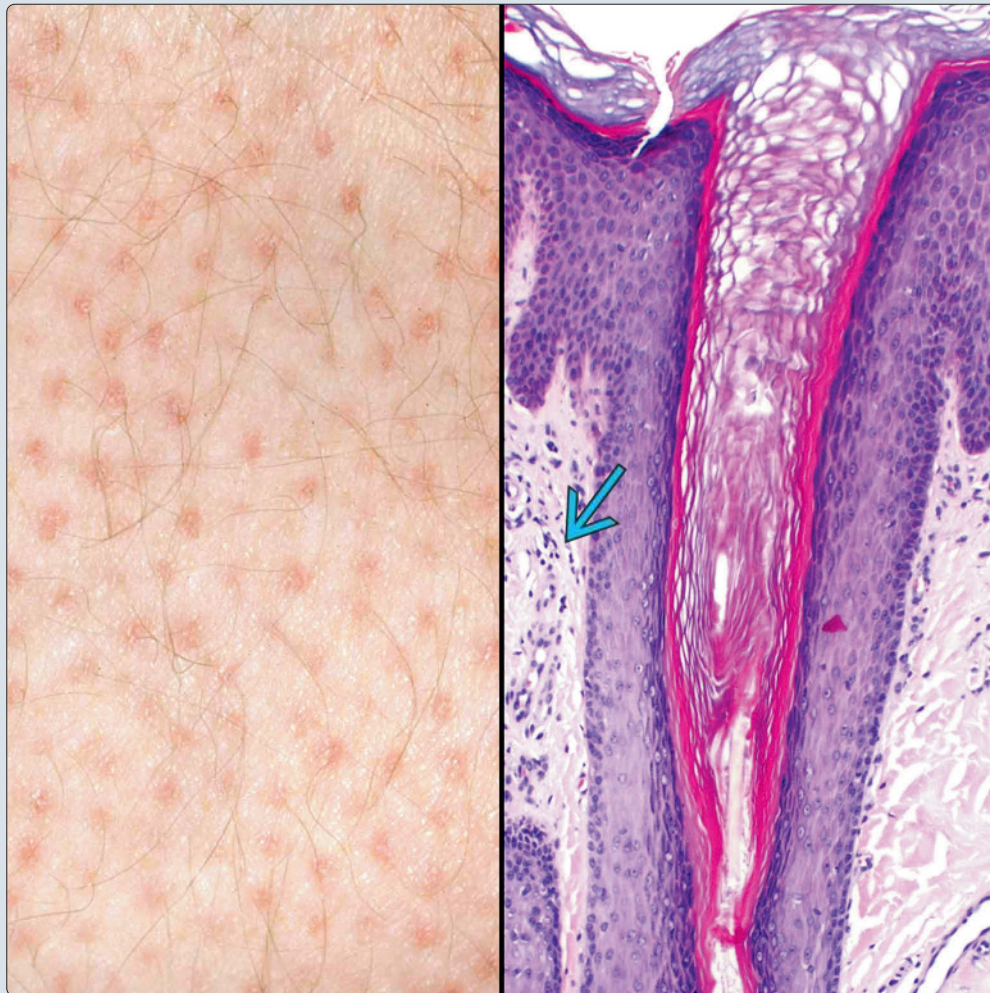
**MICROSCOPIC**

- Hyperkeratosis within and around follicle
- Follicular infundibulum is widened and expanded by hyperkeratosis
- Sparse perifollicular inflammation

**TOP DIFFERENTIAL DIAGNOSES**

- Folliculitis
  - Follicle disrupted by acute inflammation (neutrophils) or by chronic inflammation (lymphocytes and histiocytes)
- Atopic dermatitis or other eczema
  - Epidermal spongiosis
  - Perivascular inflammation, including eosinophils
- Grover disease
  - Histologically, there is focal acantholytic dyskeratosis
- Pityriasis rubra pilaris
  - Alternating zones of parakeratosis and orthokeratosis in cornified layer
- Lichen sclerosus
  - Homogenized and sclerotic collagen of papillary and reticular dermis
- Scurvy
  - Perifollicular hemorrhage
  - Corkscrew-shaped twisting of hair shaft

**Folliculocentric Keratotic Papules and Hyperkeratosis in Widened Follicular Infundibulum**



*Left: Keratosis pilaris is a common condition characterized by keratotic spiny erythematous papules centered around follicles. The upper arms and thighs are most commonly affected. Right: A follicular infundibulum is widened and filled by hyperkeratosis. There is a sparse perifollicular inflammation composed of mononuclear cells [\[5\]](#).*



## TERMINOLOGY

### Abbreviations

- Keratosis pilaris (KP)

### Synonyms

- Follicular keratosis

### Definitions

- Hyperkeratosis of hair follicle infundibula

## CLINICAL ISSUES

### Presentation

- Extremely common
  - Onset in childhood or adolescence
- Most often involves extensor surfaces of upper arms
- May also be seen on thighs and face
- Presents as spiny or keratotic erythematous papules centered on follicles
- Usually asymptomatic
- May be cosmetically distressing
- Clinical variants of KP
  - KP atrophicans
    - Group of rare genodermatoses
    - Ulerythema ophryogenes
      - Follicular keratosis and alopecia of eyebrows
    - Atrophoderma vermiculatum
      - Predominantly affects cheeks
      - Atrophic erythematous macules and depressions
    - Keratosis follicularis spinulosa decalvans
      - Scarring alopecia of hair bearing areas
- KP-like drug eruptions may be caused by BRAF inhibitors

### Treatment

- Drugs
  - Keratolytics: Urea, lactic acid, salicylic acid
  - Topical retinoids: Tretinoin, tazarotene
  - Diode or Nd:YAG laser

### Prognosis

- Usually persistent but tends to improve with age

## MICROSCOPIC

### Histologic Features

- Distended follicular infundibulum
- Hyperkeratosis within and around follicular infundibulum
- May see sparse perivascular inflammatory infiltrates

## DIFFERENTIAL DIAGNOSIS

### Folliculitis

- Usually will see pustules in addition to erythematous follicular papules
- No hyperkeratosis
- Follicle disrupted by acute inflammation (neutrophils) or by chronic inflammation (lymphocytes and histiocytes)

### Grover Disease

- Erythematous follicular papules on chest
- Elderly patients
- Histologically, there is focal acantholytic dyskeratosis

### Pityriasis Rubra Pilaris

- Widespread eruption begins as erythematous follicular papules
- Usually starts on upper body and then generalizes
- Waxy keratoderma of palms and soles
- Follicular hyperkeratosis
- Alternating zones of parakeratosis and orthokeratosis in cornified layer
- Irregular acanthosis of rete ridges

### Eczematous Dermatitis

- May see hyperkeratosis of follicle
- Can present as clinically follicular eruption
- Pruritus
- Epidermal spongiosis
- Perivascular inflammation, including eosinophils

### Lichen Sclerosus

- Follicular hyperkeratosis and plugging
- Epidermal atrophy
- Papillary dermal edema
- Homogenized and sclerotic collagen of papillary and reticular dermis

### Scurvy

- Follicular hyperkeratosis
- Perifollicular hemorrhage
- Corkscrew-shaped twisting of hair shaft
- Bleeding of gingiva

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Hyperkeratosis of follicular infundibulum leads to spiny papule clinically

### Pathologic Interpretation Pearls

- Sparse inflammation
- Infundibulum expanded by hyperkeratosis

## SELECTED REFERENCES

1. Ibrahim O et al: Treatment of keratosis pilaris with 810-nm diode laser: a randomized clinical trial. *JAMA Dermatol.* 151(2):187-91, 2015
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4. Malvankar DD et al: Keratosis follicularis spinulosa decalvans: a report of three cases. *Int J Trichology.* 7(3):125-8, 2015
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## Circumscribed Acral Hypokeratosis

## KEY FACTS

## TERMINOLOGY

- Idiopathic, acquired condition that presents usually as solitary, well-circumscribed, and erythematous depression, typically on palm

## ETIOLOGY/PATHOGENESIS

- Most likely cause is defect in maturation of keratin
  - This may be result of chronic subclinical trauma

## CLINICAL ISSUES

- Quite rare and only recently reported (2002, Perez et al)
- Approximately 30 cases have been reported in literature
- Solitary or multiple circular, depressed, asymptomatic, erythematous patches on palms or soles
  - Most patients present with single lesion
- Lesions are more commonly found on palms (only a few case reports on plantar surfaces to date)
  - Hypothenar and thenar eminences of palms are most commonly involved sites

- Treatment is generally not needed, but may be pursued for cosmetic reasons
  - Numerous different modalities have been tried with limited success



## MICROSCOPIC

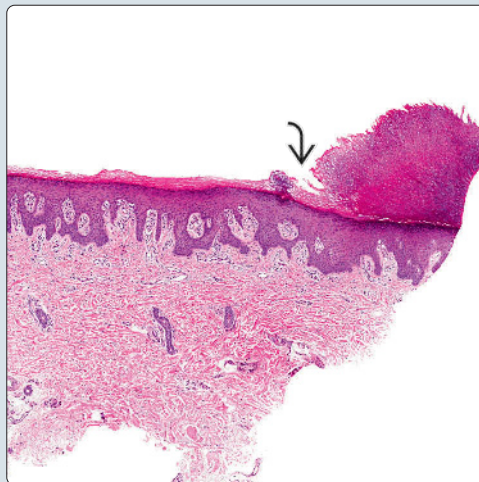
- Sharply demarcated ("punched-out") thinning of stratum corneum
  - Granular layer may diminished underlying
- Dilated and elongated dermal capillaries

## TOP DIFFERENTIAL DIAGNOSES

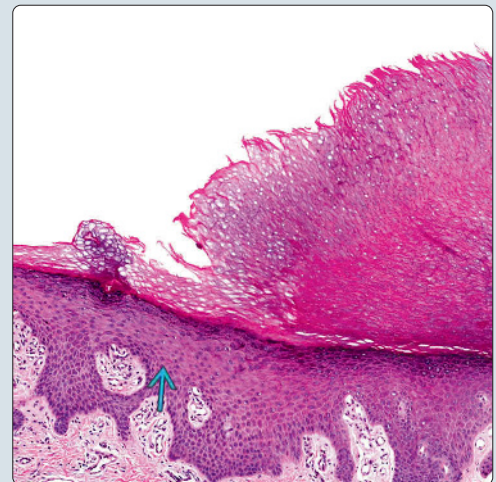
- Palmoplantar porokeratosis
  - Cornoid lamellae present (discrete columns of parakeratosis)
- Pitted keratolysis
  - Shallow pits with filamentous bacteria seen microscopically

Sharply Demarcated Thinning of Stratum Corneum




**(Left)** In acral skin, there is an abrupt drop-off in the cornified layer  that is sharply demarcated from normal skin and almost appears "punched-out." **(Right)** Note how directly beneath areas where the stratum corneum is thinned, the granular layer is much thinner  than in areas where the full thickness of the stratum corneum is preserved. Dilated and elongated dermal capillaries are also present in the dermis.

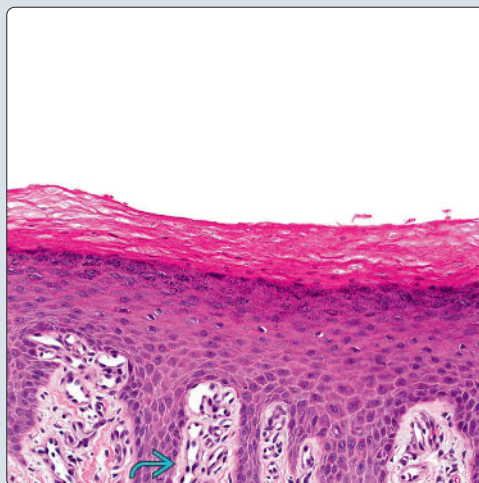


Thinning of Stratum Corneum With Underlying Hypogranulosis

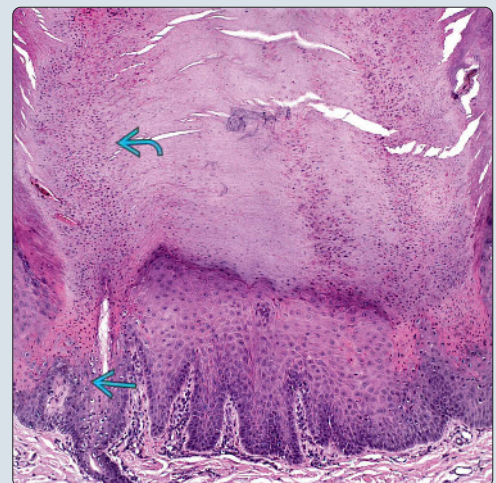


Thinned Stratum Corneum With Dilated Dermal Capillaries

**(Left)** Underneath the areas of thinned stratum corneum, dilated and elongated capillaries  are often found. It appears as if a large portion of the stratum corneum was shaved off. **(Right)** Cornoid lamellae are the hallmark of porokeratosis and are easily identifiable as columns of parakeratosis  with underlying hypogranulosis and keratinocyte dyskeratosis . The stratum corneum is not thinned.



Palmoplantar Porokeratosis With Cornoid Lamellae





## TERMINOLOGY

### Abbreviations

- Circumscribed acral hypokeratosis (CAH)

### Synonyms

- Circumscribed plantar hypokeratosis
- Circumscribed palmar hypokeratosis
- Circumscribed palmoplantar hypokeratosis

### Definitions

- Idiopathic, acquired condition that presents usually as solitary, well-circumscribed, and erythematous depression, typically on palm

## ETIOLOGY/PATHOGENESIS

### Developmental Anomaly

- Most likely cause is defect in maturation of keratin
  - May be result of chronic subclinical trauma

### Environmental Exposure

- Chronic subclinical trauma has been hypothesized by Resnick et al

### Infectious Agents

- Some hypothesize CAH may be form fruste of acral verrucae or epidermolysis bullosa

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Quite rare and only recently reported (2002, Perez et al)
  - ~ 30 cases have been reported in literature
    - Although probably more common (probably under-reported and under-recognized)
- Age
  - 30-80 years
- Sex
  - M:F ~ 1:4

### Presentation

- Solitary or multiple circular, depressed, asymptomatic, erythematous patches on palms or soles
  - Most patients present with single lesion
  - Lesions typically asymptomatic
  - Lesions are more commonly found on palms (only a few case reports on plantar surfaces to date)
- Border of lesion may be slightly elevated
- Hypothenar and thenar eminences of palms are most commonly involved sites
- Single case has been reported on nonacral site (chest)

### Treatment

- Generally not needed, but may be pursued for cosmetic reasons
- Numerous different modalities have been tried with limited success

### Prognosis

- Excellent
  - One rare case report of actinic keratosis associated with CAH probably secondary to sun exposure

## MICROSCOPIC

### Histologic Features

- Sharply demarcated ("punched-out") thinning of stratum corneum
  - Granular layer may diminished underlying
- Dilated and elongated dermal capillaries

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Histopathologic findings in CAH are quite unique, limiting histopathologic differential diagnosis
  - Lack of awareness of entity is biggest risk for misdiagnosis
- Palmoplantar porokeratosis
  - Cornoid lamellae present (discrete columns of parakeratosis)
    - Dyskeratotic and vacuolated keratinocytes typically present underneath
  - Focal hypogranulosis is present underneath cornoid lamellae
    - vs. no changes in granular layer or rare reports of hypogranulosis in CAH
  - Stratum corneum unremarkable between cornoid lamellae (no thinning as in CAH)
- Pitted keratolysis
  - Pit or dell in cornified layer is less dramatic and abrupt
  - Filamentous bacteria can be seen in cornified layer

### Clinical

- Palmoplantar porokeratosis
  - Not typically erythematous (usually flesh-colored)
  - Presence of cornoid lamella
- Squamous cell carcinoma/Bowen disease
  - No sharply demarcated border clinically (poorly demarcated with ill-defined edge)
  - Induration
- Friction blister
  - Very regular edge and circular in shape
  - Blister would often be present on surface
  - Eroded blisters may mimic, but hanging fringe of epidermis should still be present
- Palmoplantar psoriasis
  - Hyperkeratotic
  - Silvery white scale
  - May be fissured on acral sites
- Pitted keratolysis
  - Complex network of shallow pits on acral surface of feet
  - Usually background of hyperhidrosis

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## KEY FACTS

## TERMINOLOGY

- Inflammatory linear verrucous epidermal nevus (ILVEN)

## CLINICAL ISSUES

- Site
  - Legs, thighs, and buttocks most frequently affected
  - Left side of body is more commonly involved
  - May be bilateral
- Presentation
  - Intensely pruritic
  - Persistent, scaly, linear lesion with erythema, which follows Blaschko lines
- Epidemiology
  - Usually presents in infants and children
  - Affects females more often than males
- Prognosis
  - No significant morbidity or mortality



## MICROSCOPIC

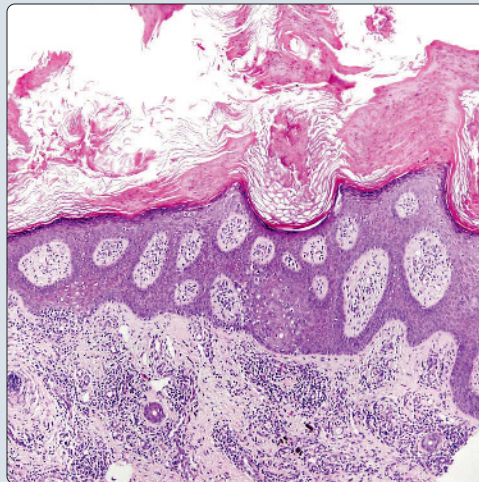
- Sharply demarcated with psoriasiform hyperplasia and thickened rete ridges
- Hyperkeratosis with alternating orthokeratosis and parakeratosis
- Absence of granular layer under areas of parakeratosis
- Thickened granular layer under areas of orthokeratosis
- Usually slight spongiosis with mild lymphocyte epidermotropism
- Mild perivascular lymphocytic infiltrate
- Munro microabscesses may be complicating feature
- No HPV virus cytopathic effect

## TOP DIFFERENTIAL DIAGNOSES

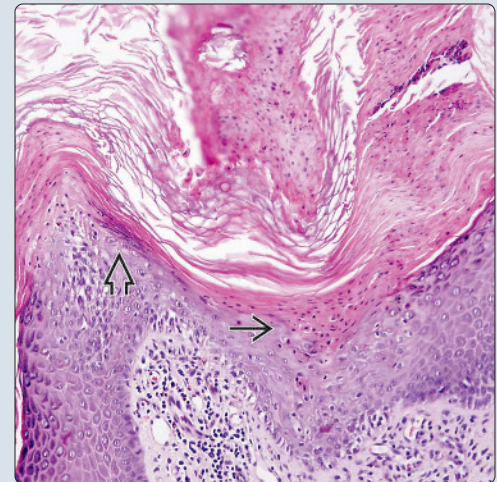
- Linear psoriasis
- Chronic spongiotic dermatitis
- Condyloma acuminatum
- Epidermal nevus
- Lichen striatus

## Alternating Ortho- and Parakeratosis


(Left) At low power, there is pronounced acanthosis with thickened rete ridges. Alternating orthokeratosis and parakeratosis are also readily appreciated. (Right) Underneath the areas of parakeratosis, there is a diminished or absent granular layer . The orthokeratosis overlies a thickened granular layer .

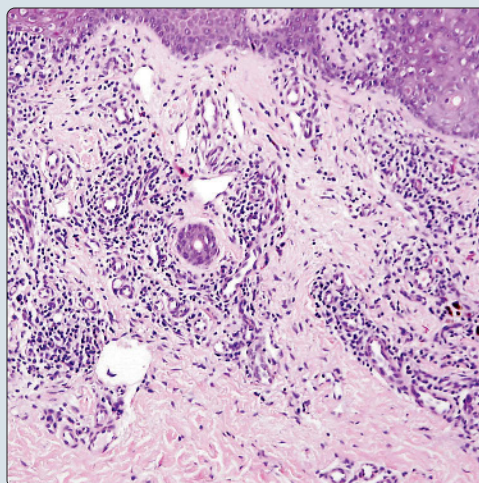


## Absent Granular Layer Beneath Parakeratosis

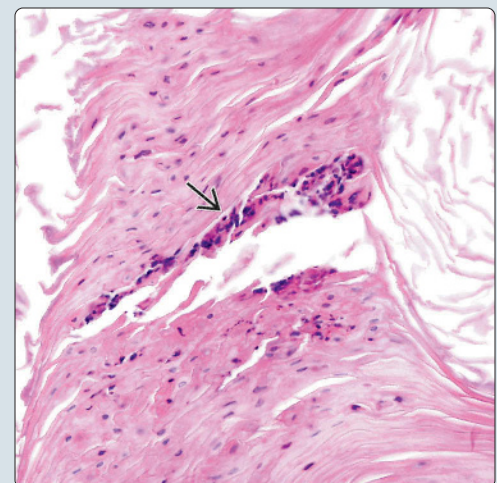


## Dermal Infiltrate

(Left) There is a lymphocytic infiltrate in the papillary dermis. (Right) Munro microabscesses  can be seen in inflammatory linear verrucous epidermal nevus (ILVEN). This may lead to diagnostic confusion with linear psoriasis, and the remaining features of ILVEN are needed to make a definitive distinction.



## Munro Microabscess





**TERMINOLOGY****Abbreviations**

- Inflammatory linear verrucous epidermal nevus (ILVEN)

**Definitions**

- Linear, intensely pruritic, scaly lesion following lines of Blaschko

**CLINICAL ISSUES****Site**

- Legs, thighs, and buttocks most frequently affected
- Left side of body is more commonly involved
- May be bilateral

**Presentation**

- Usually presents in infants and children
- Affects females more often than males
- Intensely pruritic
- Persistent, scaly, linear lesion with erythema, which follows Blaschko lines

**Treatment**

- Surgical approaches
  - Complete excision has been successful in some cases
  - May require skin grafts after excision
- Drugs
  - Topical corticosteroids, vitamin D3 analogues, and others with limited success
  - Does not respond well to biologic agents usually used in treatment of psoriasis
- Other modalities
  - CO<sub>2</sub> laser therapy, cryotherapy with liquid nitrogen

**Prognosis**

- No significant morbidity or mortality

**MICROSCOPIC****Histologic Features**

- Sharply demarcated with psoriasiform hyperplasia and thickened rete ridges
- Hyperkeratosis with alternating orthokeratosis and parakeratosis
- Absence of granular layer under areas of parakeratosis
- Thickened granular layer under areas of orthokeratosis
- Usually slight spongiosis with mild lymphocyte epidermotropism
- Mild perivascular lymphocytic infiltrate
- Munro microabscesses may be complicating feature
- No HPV virus cytopathic effect

**DIFFERENTIAL DIAGNOSIS****Linear Psoriasis**

- Munro microabscesses are more consistent feature
- Confluent parakeratosis with decreased or absent granular layer
- Psoriasiform hyperplasia with thin rete ridges
- Clinically not pruritic

**Chronic Spongiotic Dermatitis**

- Acanthosis without psoriasiform hyperplasia
- No alternating parakeratosis and orthokeratosis
- If areas of neutrophil infiltration, they are usually accompanied by other signs of scratching

**Condyloma Acuminatum**

- Acanthosis without psoriasiform hyperplasia
- Usually thickened granular layer
- Vague papillomatosis of epidermis
- Often at least focal HPV viral cytopathic features
- May have intraepidermal dysplasia or even foci of invasive carcinoma

**Epidermal Nevus**

- Papillomatosis with orthokeratosis usually
- Rete ridge elongation but not psoriasiform hyperplasia
- No alternation of orthokeratosis and parakeratosis with underlying granular layer changes
- Resembles squamous papilloma or seborrheic keratosis

**Lichen Striatus**

- Spongiosis with lymphocytic exocytosis
- Usually lichenoid inflammation with interface changes as well
- Satellite cell necrosis
- Lymphocytes also involve sweat glands
- Clinically not pruritic

**DIAGNOSTIC CHECKLIST****Clinically Relevant Pathologic Features**

- Intense pruritus
- Linear, scaly lesion, which occurs along Blaschko lines
- Usually unilateral, but may be bilateral
- Usually affects legs, thighs, and buttocks

**Pathologic Interpretation Pearls**

- Psoriasiform hyperplasia
- Alternating orthokeratosis and parakeratosis
- Decreased granular layer under parakeratotic foci
- Increased granular layer under orthokeratotic foci

**SELECTED REFERENCES**

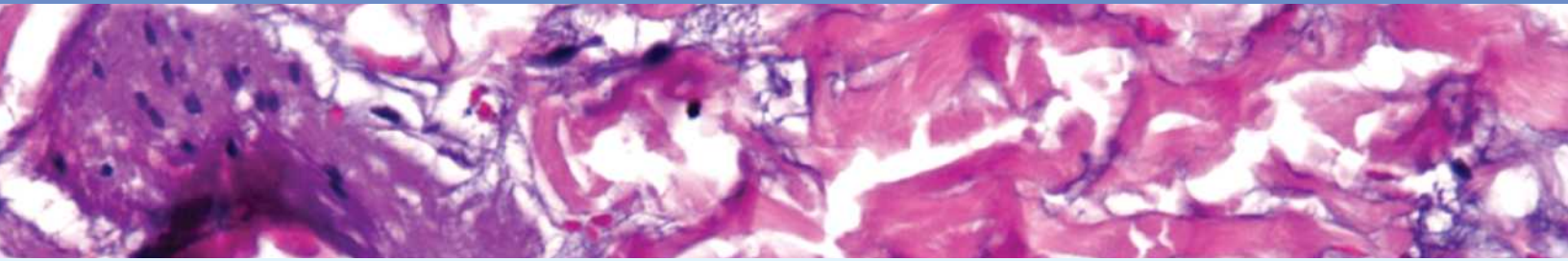
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3. Conti R et al: Inflammatory linear verrucous epidermal nevus: why a combined laser therapy. *J Cosmet Laser Ther.* 15(4):242-5, 2013
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## SECTION 15

# Disorders of Pigmentation



Vitiligo	470
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## KEY FACTS

## TERMINOLOGY

- Acquired loss of melanocytes and melanin pigment leading to 1 or multiple areas of leukoderma

## ETIOLOGY/PATHOGENESIS

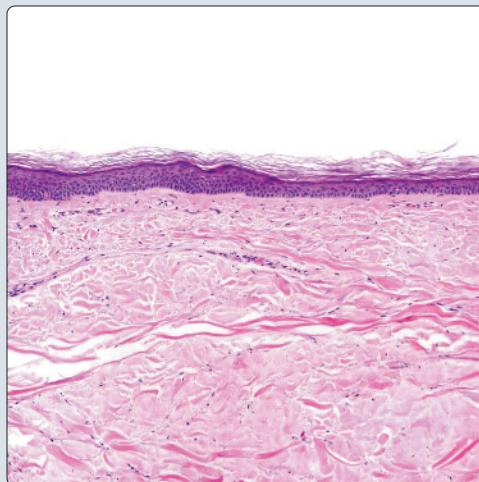
- Multiple associations
  - Inflammatory and autoimmune diseases
  - Medications/therapies
- Various theories of pathogenesis
  - Autoimmune hypothesis
  - Reactive oxygen species model
  - Viral theory
  - Genetic
  - Others

## CLINICAL ISSUES

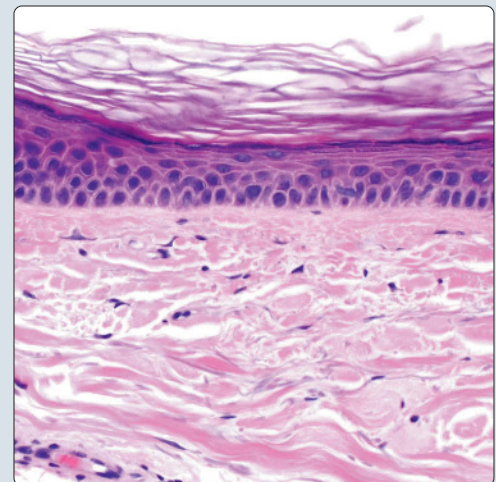
- Usually starts in single location and progresses to involve multiple sites

- Flexural areas, mouth, genitalia, orbits, and bony prominences are most commonly affected
- Koebner phenomenon may be present
- Border of leukoderma may be erythematous or hyperpigmented
  - Active inflammatory border
- Hair shafts often retain pigment until late in disease process
- Repigmentation usually begins in perifollicular distribution
- Incidence
  - Affects between 1-2% of population
- Ethnicity
  - Affects all races
- Age
  - All ages are affected but most frequently seen in 2nd, 3rd, and 4th decades

Normal-Appearing Epidermis and Dermis

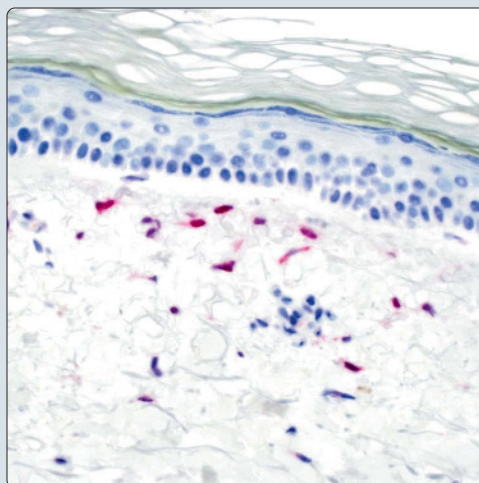


Absence of Melanocytes



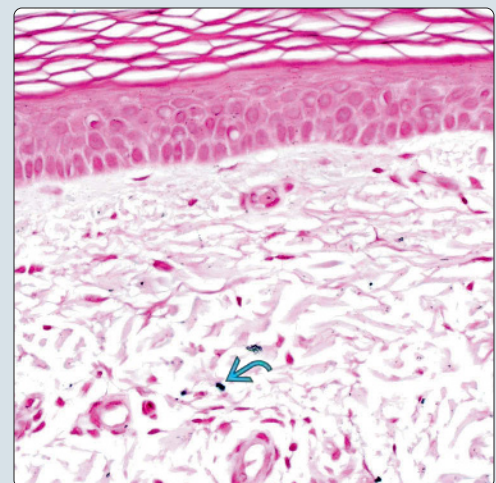
**(Left)** Without an appropriate clinical history, it would be easy to overlook the changes seen in vitiligo. The epidermis and dermis appear normal at lower power. **(Right)** Upon close inspection at higher power, no melanocytes are identified. No significant inflammation is present. To confirm the diagnosis, further stains are required.

Melan-A Negative in Epidermis



**(Left)** A Melan-A red immunostain is negative for melanocytes in the epidermis. Dendritic cells in the dermis are positive, and they serve as an internal tissue control. Occasional epidermal dendritic cells may be present, but no regularly spaced melanocytes should be identified. **(Right)** A Fontana-Masson stain is negative for melanin. In addition to the absence of melanocytes, there should not be epidermal melanin in keratinocytes in classical vitiligo. There is some positive staining within dermal histiocytes.

No Melanin Identified With Fontana-Masson





## TERMINOLOGY

### Definitions

- Acquired loss of melanocytes and melanin pigment leading to 1 or multiple areas of leukoderma

## ETIOLOGY/PATHOGENESIS

### Multiple Associations

- Inflammatory and autoimmune diseases
  - Hashimoto thyroiditis, autoimmune gastritis, alopecia areata, diabetes mellitus, Addison disease, and more
- Medications/therapies
  - PUVA, interferon alpha, chloroquine, imiquimod, and more

### Most Popular Theories

- Autoimmune hypothesis
  - Association with autoimmune diseases
  - Cell-mediated cytotoxicity
  - Humoral immunity
- Reactive oxygen species (ROS) model
  - Melanocytes more susceptible to damage from ROS
- Viral theory
  - Increased prevalence in hepatitis C patients
- Other theories exist but complete discussion of them is beyond scope of this chapter

## CLINICAL ISSUES

### Presentation

- Usually starts in single location and progresses to involve multiple sites
- Flexural areas, mouth, genitalia, orbits, and bony prominences are most commonly affected
- Koebner phenomenon may be present
- Areas of leukoderma may sunburn
  - May also tan in areas between leukoderma and normal pigmentation: Implies active disease
    - Trichome vitiligo
- Border of leukoderma may be erythematous or hyperpigmented
  - Active inflammatory border
- Hair shafts often retain pigment until late in disease process
- Repigmentation usually begins in perifollicular distribution
- Numerous variants (most common are listed below)
  - Localized
    - Focal, segmental, mucosal, and follicular forms
  - Generalized
    - Acrofacial, vulgaris, universalis, and mixed forms

### Treatment

- Drugs
  - Topical corticosteroids, others
- Light
  - PUVA

### Prognosis

- Repigmentation may occur spontaneously or after treatment

### Incidence

- Affects between 1-2% of population
- Up to 40% of affected individuals have family members with vitiligo

### Ethnicity

- Affects all races
  - Leukoderma is more noticeable in patients with darker skin
  - Unknown if vitiligo is truly more common in darker skinned individuals

### Age

- All ages are affected but most frequently seen in 2nd, 3rd, and 4th decades

## MICROSCOPIC

### Histologic Features

- Complete loss of melanocytes and melanin along basal layer
- ± mild superficial perivascular lymphohistiocytic infiltrate

## ANCILLARY TESTS

### Histochemistry

- Fontana-Masson stain
  - Absent melanin in areas of leukoderma

### Immunohistochemistry

- S100, Melan-A, MART-1, SOX10, MITF, HMB-45, etc.
  - Melanocyte markers show absent or markedly decreased melanocytes
  - S100 will still be positive in epidermal Langerhans cells

## DIFFERENTIAL DIAGNOSIS

### Clinical/Histopathological

- Idiopathic guttate hypomelanosis
  - Most lesions < 5 mm
  - No spontaneous repigmentation
  - Variable loss of melanin and melanocytes
- Postinflammatory hypopigmentation
  - Occurs after inflammatory dermatosis
  - Reduced melanin in basal layer
- Pityriasis alba
  - Occurs in children, often with atopic diathesis
  - Mild loss of melanin, but melanocytes are preserved
  - Mild pigment incontinence
- Pityriasis versicolor (tinea versicolor)
  - Multiple patches of hypopigmented skin with fine scale in darker skinned individuals
    - Lighter skinned people tend to have hyperpigmented areas
  - Caused by *Malassezia* species fungi

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# Postinflammatory Pigment Alteration

## KEY FACTS

### ETIOLOGY/PATHOGENESIS

- Postinflammatory (PI) hyperpigmentation: Damage to keratinocytes and melanocytes results in pigment incontinence and phagocytosis of melanin by melanophages
- PI hypopigmentation: Possibly due to decreased transfer of melanin from melanocytes to keratinocytes

### CLINICAL ISSUES

- Can occur in all skin types
- Both changes are most noticeable in dark skinned individuals (phototypes III to VI)
- Hyper- or hypopigmented macules and patches following inflammatory or infectious process
- May be self-resolving, symptoms can last weeks to years

### MACROSCOPIC

- Lesions follow distribution of initial inflammatory process or area of trauma

### MICROSCOPIC

- Increased or decreased pigmentation in basal layer of epidermis
- PI hypopigmentation: Superficial lymphohistiocytic infiltrate, confocal laser scanning microscopy reveals melanophages
- PI hyperpigmentation: Melanophages in papillary dermis

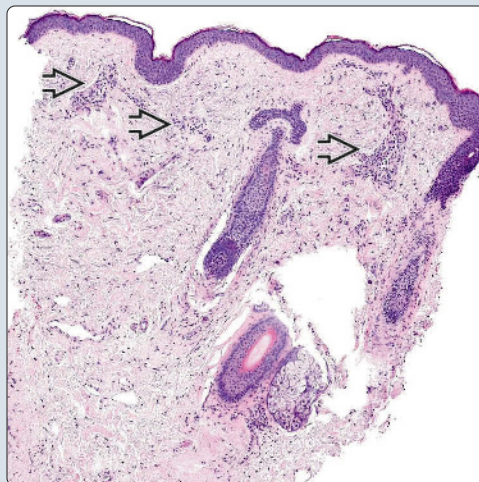
### TOP DIFFERENTIAL DIAGNOSES

- Vitiligo
- Melasma
- Nevus depigmentosus
- Drug induced hyperpigmentation
- Idiopathic guttate hypomelanosis

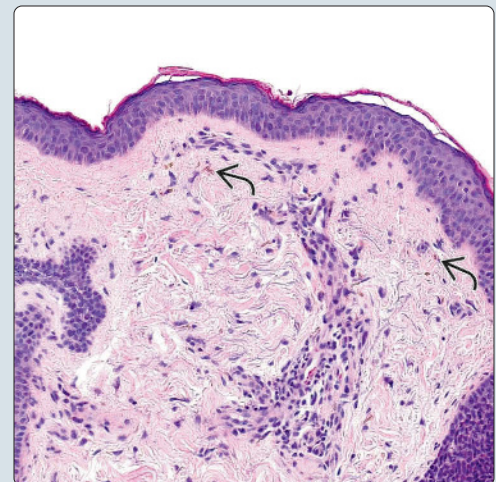
**Superficial Perivascular Infiltrate**

*(Left) A low-power view of postinflammatory pigment alteration demonstrates moderate perivascular superficial dermal inflammatory cell infiltrate*

*(Right) Mild lymphohistiocytic perivascular inflammatory cell infiltrate in the superficial dermis is seen in this biopsy of postinflammatory hyperpigmentation. Pigment incontinence can be seen.*

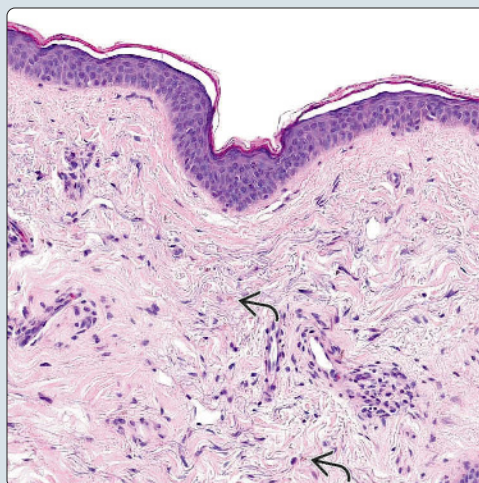


**Lymphohistiocytic Perivascular Infiltrate**

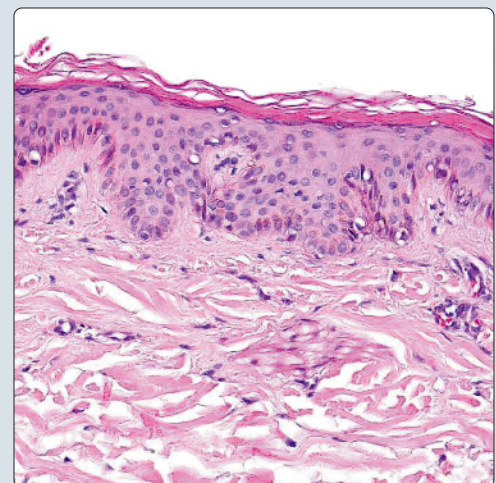


**Perivascular Infiltrate With Pigment Incontinence**

*(Left) A biopsy of postinflammatory pigment alteration demonstrates a perivascular lymphohistiocytic dermal infiltrate with overlying unremarkable epidermis. Subtle pigment incontinence can also be appreciated. (Right) In this case of postinflammatory hyperpigmentation, subtle basal layer hyperpigmentation can be seen on high power.*



**Basal Layer Hyperpigmentation**





## TERMINOLOGY

### Abbreviations

- Postinflammatory (PI)

### Synonyms

- PI hypopigmentation, PI hyperpigmentation (PI melanosis)

### Definitions

- PI hypopigmentation
  - Decreased pigmentation of skin following inflammatory rash or infection
- PI hyperpigmentation
  - Increased pigmentation of skin following inflammatory dermatoses

## ETIOLOGY/PATHOGENESIS

### Postinflammatory Hyperpigmentation

- Damage to keratinocytes and melanocytes results in pigment incontinence and phagocytosis of melanin by melanophages
- Occurs in setting of
  - Lichen planus, lichenoid drug eruptions, fixed drug eruptions, lupus erythematosus, contact dermatitis, psoriasis
  - Trauma (chemical peels, acne, burns, phototoxicity, arthropod assault)

### Postinflammatory Hypopigmentation

- Possibly due to decreased transfer of melanin from melanocytes to keratinocytes
- Occurs in setting of
  - Eczema, psoriasis, blistering disorders, pityriasis lichenoides
  - Infections: Pityriasis versicolor, tuberculoid leprosy, postkala-azar dermal leishmaniasis, pityriasis alba, syphilis
  - Sarcoidosis, graft-vs.-host disease

## CLINICAL ISSUES

### Epidemiology

- Occurs at any age, affecting men and women equally
- Can occur in all skin types; both changes are most noticeable in dark skinned individuals (phototypes III to VI)

### Presentation

- Size and shape of lesions range from macules to patches
  - Correlating with distribution of causative inflammatory process or insult
- PI hypopigmentation
  - Ranges from lighter pigmentation to complete loss of pigment (depigmentation)
- PI hyperpigmentation
  - Ranges from light brown (pigment within epidermis) to darker gray, blue, and black (pigment within dermis)

## MACROSCOPIC

### General Features

- Lesions follow distribution of initial inflammatory process or area of trauma
- PI hypopigmentation

- Brown, gray, blue, or black macules and patches
- PI hyperpigmentation
  - Lighter colored (light brown to bone white) macule and patches

## MICROSCOPIC

### Histologic Features

- PI hypopigmentation
  - Focal reduction in basal cell layer pigmentation
  - Number of melanocytes usually normal
  - Superficial lymphohistiocytic infiltration
  - No histologic evidence of causative disorder (psoriasis, blistering disorder, tinea)
- PI hyperpigmentation
  - Increased basal cell layer pigmentation
  - Giant melanosomes may be present in epidermis
  - Melanophages in papillary dermis
  - There may be subtle clues to causative process
    - Presence of colloid bodies suggest prior interface reaction

## ANCILLARY TESTS

### Histochemistry

- Fontana-Masson stain highlights melanin

## DIFFERENTIAL DIAGNOSIS

### Melasma

- Typically lesions are localized to face
- Increased melanin in basal layer of epidermis &/or dermis with presence of melanophages (most commonly both locations)

### Vitiligo

- Decreased or absent melanocytes and melanin in basal layer, generally requires special stains

### Nevus Depigmentosus

- No melanophages on confocal microscopy

### Drug-Induced Hyperpigmentation

- Nonmelanin deposits in dermis

### Idiopathic Guttate Hypomelanosis

- Drop-like, white macules on forearms and legs
- Histology shows epidermal atrophy

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## Pityriasis Alba

## KEY FACTS

## TERMINOLOGY

- Relatively common skin disorder characterized by hypopigmented patches or thin plaques with slight scale typically found in children on face (esp. cheeks), neck, &/or shoulders

## CLINICAL ISSUES

- Well- or ill-defined white (hypopigmented) patches or thin plaques with overlying fine scale
- Almost always involves cheeks and/or upper outer arms
- Occurs almost exclusively in preadolescent children

## MICROSCOPIC

- Biopsy usually done to rule out hypopigmented mycosis fungoides
- Usually included with other "minimal" or "invisible" dermatoses
- Irregular or reduced melanin pigment deposition along basal epidermal layer

- Early lesions
  - Nonspecific findings
  - Follicular dilatation, follicular plugging, spongiosis, dermal edema, and superficial perivascular lymphocytic infiltrate
- Late lesions
  - Nonspecific findings
  - Hyperkeratosis, focal parakeratosis and spongiosis

## TOP DIFFERENTIAL DIAGNOSES

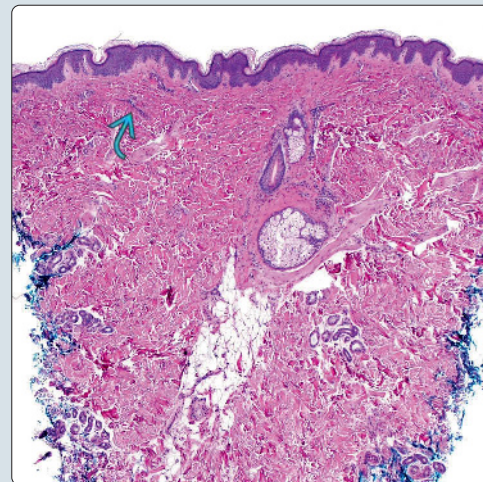
- Histopathologic
  - Other "invisible" dermatoses
    - May show obvious clinical disease but demonstrate very little findings on biopsy
    - Vitiligo
    - Viral exanthem
    - Cutis laxa
    - Others

## Ill-Defined Hypopigmented Patch

(Left) Pityriasis alba presents as ill-defined white (hypopigmented) patches or thin plaques with overlying fine scale commonly on the upper outer arms (or cheeks) of preadolescent patients. (Courtesy L. Wilson, MD.) (Right) Low-power view from a biopsy of pityriasis alba demonstrates nonspecific changes. There is a slight superficial perivascular infiltrate that is barely appreciable.

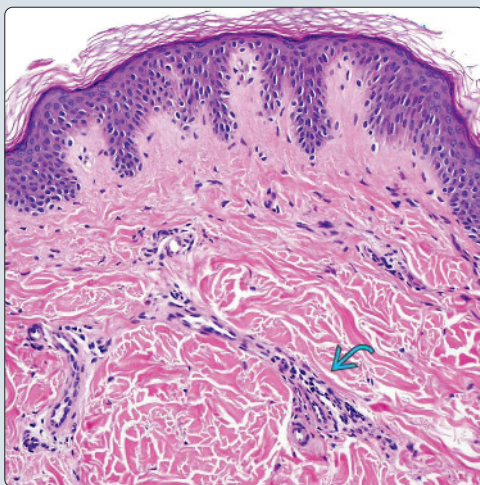


## Minimal Obvious Changes on Biopsy

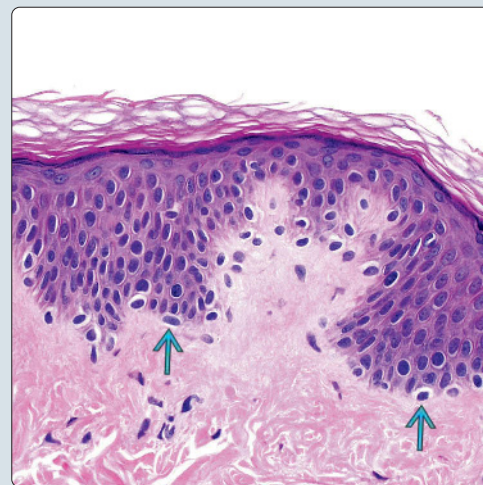


## Sparse Superficial Perivascular Infiltrate

(Left) Higher power view demonstrates a mild perivascular lymphocytic infiltrate. There is also very slight acanthosis. No other significant changes are identifiable. (Right) On higher power view, the melanocytes appear normal in number, but there does appear to be a decrease in the amount of melanin pigment in the basal layer. Vitiligo would show a loss of melanocytes in addition to decreased pigment.



## Reduced Melanin Pigment Along Basal Layer





## TERMINOLOGY

### Abbreviations

- Pityriasis alba (PA)

### Synonyms

- Eczema

### Definitions

- Relatively common skin disorder characterized by hypopigmented patches or thin plaques with slight scale typically found in children on face (esp. cheeks), neck, &/or shoulders

## ETIOLOGY/PATHOGENESIS

### Unknown

- Some factors have been implicated in proneness to develop disease
  - Dry skin
  - History of atopy
  - Nutritional deficiency (such as anemia, others)
  - Infections

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Unknown but prevalence estimated anywhere from up to 5-10% of school children
- Age
  - Occurs almost exclusively in preadolescent children
    - Can persist into adulthood
  - Rarely occurs in young adults
- Sex
  - Possible slight male predominance
- Ethnicity
  - Occurs in all ethnicities
    - However, may be more apparent and bothersome in darker skinned patients
- Seasonal variation
  - Reported to be more common and more apparent in cold weather
  - Exacerbation can be seen in beginning of winter
  - Sun exposure in summer or spring may make lesions more apparent clinically

### Presentation

- Well- or ill-defined white (hypopigmented) macules, patches or thin plaques with overlying fine scale
  - Central hyperpigmentation may occasionally be present
  - Rarely, lesions can become widespread (generalized pityriasis alba)
    - Usually seen in young adults but also reported in infants
- Pruritus may also rarely be reported
- Almost always involves cheeks and upper outer arms

### Treatment

- Not needed; lesions resolve spontaneously
- In darker skinned patients, avoidance of sun exposure may help reduce darkening of surrounding skin

### Prognosis

- Excellent; lesions are completely benign

## MICROSCOPIC

### Histologic Features

- Biopsy usually done to rule out hypopigmented mycosis fungoides
- Usually included with other "minimal" or "invisible" dermatoses
  - So named due to lack of distinguishing or significant histopathologic features
- Irregular or reduced melanin pigment deposition along basal epidermal layer
  - Number of melanocytes should be normal
    - And should not differ between lesional and nonlesional skin
- Early lesions
  - Nonspecific findings
  - Follicular dilatation, follicular plugging, spongiosis, dermal edema, and superficial perivascular lymphocytic infiltrate
- Late lesions
  - Nonspecific findings
    - Hyperkeratosis, focal parakeratosis and spongiosis
- Most common findings include
  - Hyperkeratosis
  - Parakeratosis
  - Acanthosis (usually slight)
  - Spongiosis
  - Superficial perivascular lymphocytic infiltrate

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Other "invisible" dermatoses
  - May show obvious clinical disease but demonstrate very little findings on biopsy
    - Biopsy may appear similar to normal skin
  - Includes numerous diseases such as
    - Vitiligo
      - ◻ Biopsies of vitiligo demonstrate decreased basal layer pigment and complete absence of melanocytes
      - ◻ Pityriasis alba demonstrates normal number of melanocytes
    - Viral exanthem
      - ◻ No decreased basal layer pigment
    - Others
  - Differentiation of these diseases is often contingent on having good clinical history from clinician
    - In biopsies with minimal changes without good clinical history, call to clinician is often of paramount importance to arrive at correct diagnosis or differential

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## Becker Nevus

## KEY FACTS

## TERMINOLOGY

- Variant of smooth muscle hamartoma with hypertrichosis and hyperpigmentation, often found on shoulder of adolescent males

## CLINICAL ISSUES

- Most often presents in adolescence following puberty
- Often seen on shoulder girdle or trunk
- Well-demarcated, but irregular, tan to dark brown, slightly raised plaque, often with hypertrichosis
- Usually solitary; wide variety in size though typically > 10 cm
- Rarely associated hypoplasia of ipsilateral breast/arm, scoliosis, spina bifida, or with accessory areola/scrotum (**Becker nevus syndrome**)

## MICROSCOPIC




- Normal number of melanocytes with increased melanosomes within keratinocytes
- Often with associated dermal smooth muscle hamartoma

- Increased basal layer pigmentation
- Regular elongation of rete ridges
- $\pm$  epidermal papillomatosis/acanthosis

## TOP DIFFERENTIAL DIAGNOSES

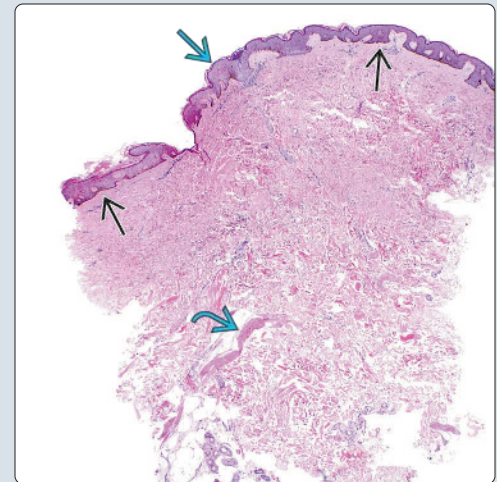
- Congenital melanocytic nevus
  - Increased melanocytes, often tracking along neurovascular, adnexal structures or extending in single-file through collagen bundles
- Smooth muscle hamartoma
  - Should demonstrate typical smooth muscle bundles within dermis without significant hypertrichosis or hyperpigmentation
- Plexiform neurofibroma
  - Schwann cells, fibroblasts, perineurial cells, and mast cells growing in plexiform growth pattern
- Café au lait macule
  - Evidence of epidermal changes, smooth muscle or hypertrichosis all favor diagnosis to Becker nevus

Hyperpigmentation and Hypertrichosis Within Pigmented Patch





(Left) Photograph shows hyperpigmentation and hypertrichosis within a large, solitary, well-demarcated, but irregular, patch. The presence of underlying smooth muscle may produce a thin plaque. Changes during puberty are a hallmark of this entity. (Right) Low-power view of a biopsy of Becker nevus demonstrates basal layer hyperpigmentation , mild papillomatosis , regular elongation of rete ridges, and a dermal proliferation of smooth muscle bundles .

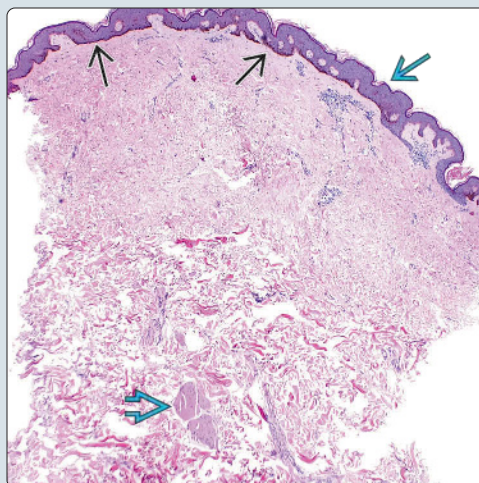


Basal Layer Hyperpigmentation and Smooth Muscle Bundles

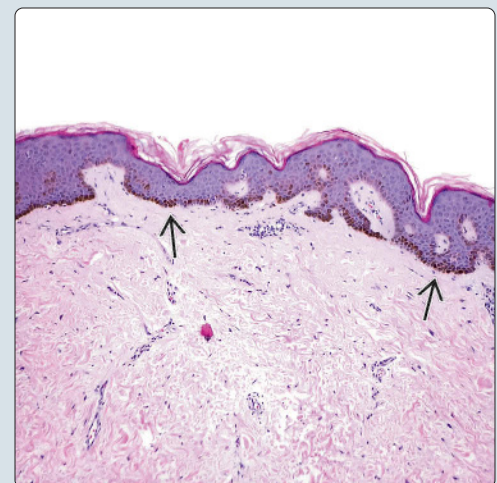


Basal Layer Hyperpigmentation and Papillomatosis

(Left) Mild papillomatosis  with basilar hyperpigmentation  and regular elongation of rete ridges is typical of Becker nevus. There is a focus of smooth muscle  in the deep dermis. At times the smooth muscle proliferation is much more prominent. (Right) Confluent basilar hyperpigmentation  with rete ridge elongation and without an increase in melanocytes or melanocytic nests is typical for Becker nevus.



Regular Elongation of Rete Ridges With Basal Layer Hyperpigmentation





**TERMINOLOGY****Synonyms**

- Becker melanosis
- Nevoid melanosis
- Pigmented hairy epidermal nevus

**Definitions**

- Variant of smooth muscle hamartoma with hypertrichosis and hyperpigmentation, often found on shoulder of adolescent males

**ETIOLOGY/PATHOGENESIS****Developmental Anomaly**

- Ectodermal and mesodermal organoid hamartoma
- May be congenital or acquired, often becomes noticeable or more prominent during puberty, suggesting hormonal influences

**CLINICAL ISSUES****Epidemiology**

- Age
  - Most often presents in adolescence following puberty
- Sex
  - Much more common in males (M:F = 6:1)

**Site**

- Often seen on shoulder girdle or trunk

**Presentation**

- Well-demarcated, but irregular, tan to dark brown, slightly raised plaque, often with hypertrichosis
- Usually solitary; wide variety in size though typically > 10 cm
- Rarely associated hypoplasia of ipsilateral breast/arm, scoliosis, spina bifida, or with accessory areola/scrotum (**Becker nevus syndrome**)

**Treatment**

- As lesions generally asymptomatic, no treatment is required
- Laser therapy
  - Variety of laser therapy for both hypertrichosis and hyperpigmentation has been employed with variable success

**Prognosis**

- Malignant transformation occurs extremely rarely, if ever

**MICROSCOPIC****Histologic Features**

- ± epidermal papillomatosis/acanthosis
- Increased basal layer pigmentation
- Regular elongation of rete ridges
- Normal number of melanocytes with increased melanosomes within keratinocytes
- Often with associated dermal smooth muscle hamartoma
- ± hypertrichosis

**DIFFERENTIAL DIAGNOSIS****Congenital Melanocytic Nevus**

- Increased melanocytes, often tracking along neurovascular, adnexal structures or extending in single-file through collagen bundles
- Clinically, has more mammillated surface; hair is more coarse

**Smooth Muscle Hamartoma**

- Exists along spectrum with Becker nevus
- Should demonstrate typical smooth muscle bundles within dermis without significant hypertrichosis or hyperpigmentation

**Plexiform Neurofibroma**

- Pathognomonic of neurofibromatosis type 1 (axillary freckling, café au lait spots, Lisch nodules, cutaneous neurofibromas)
- Schwann cells, fibroblasts, perineurial cells, and mast cells growing in plexiform growth pattern along nerve fascicles

**Café Au Lait Macule**

- In absence of hypertrichosis, may be difficult to distinguish from café au lait macule
- Evidence of epidermal changes, smooth muscle or hypertrichosis all favor diagnosis to Becker nevus

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## Melasma

## KEY FACTS

## TERMINOLOGY

- Pigmentary disorder characterized by symmetric hyperpigmented macules and patches typically on face

## CLINICAL ISSUES

- Average age is around 30 years for both men and women
- Much more common in women
- More common in darker skin types (Fitzpatrick types III, IV and V)
- Presents as brownish macules with irregular contours on sun-exposed areas
- Most effective 1st-line treatment
  - Sun avoidance, sunscreen use, and triple therapy

## MICROSCOPIC


- Increased deposits of melanin in both epidermis and dermis (within dermal melanophages)
- Mild perivascular lymphohistiocytic infiltrate  $\pm$  increased mast cells

- Number of melanocytes is not increased
  - But melanocytes are enlarged and often show greater number of dendrites
- Diagnosis is usually made clinically, and histopathologic analysis is only rarely required

## TOP DIFFERENTIAL DIAGNOSES

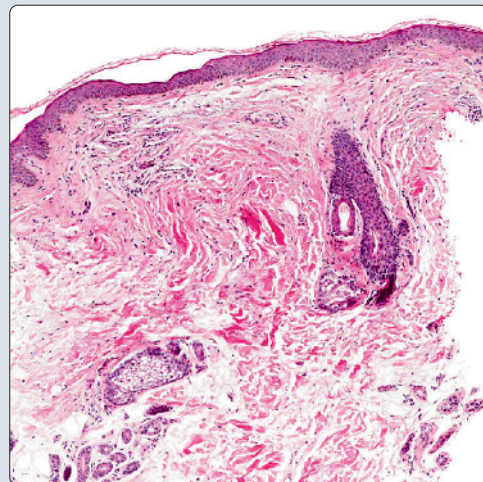
- Solar lentigo (and other forms of lentigo)
  - Typically shows bud-like elongation of rete ridges with increased pigment at base of keratinocytic buds
- Postinflammatory hyperpigmentation
  - Majority of cases have clinical history of preceding inflammatory condition (most patients remember, some may not)
- Drug-induced hyperpigmentation
  - More common on extremities than face but can occur on face
- Ochronosis
  - Banana-shaped fibers in dermis

## Light Brown Macular Areas of Hyperpigmentation





(Left) Macular, well-demarcated, light brown hyperpigmentation  is shown in a woman who had taken birth control pills in the past. Note how these lesions are photodistributed, as are most cases of melasma. (Right) From low power, a biopsy of melasma demonstrates a sparse, superficial perivascular infiltrate.

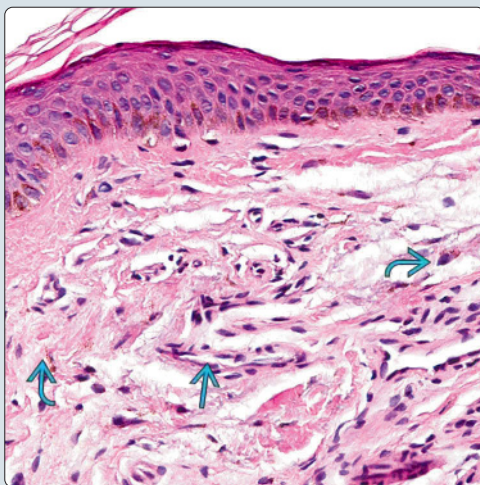


## Sparse Superficial Perivascular Infiltrate

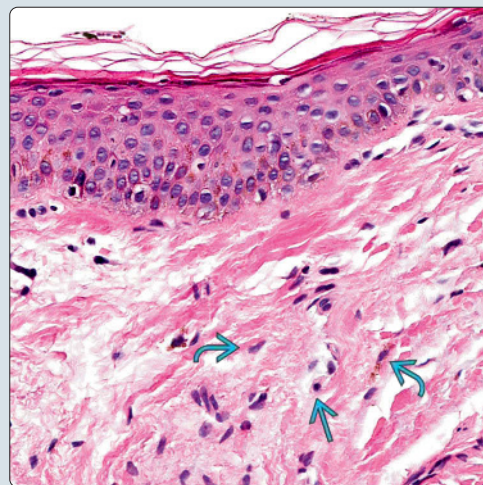


## Increased Epidermal and Dermal Melanin

(Left) Increased epidermal and dermal  melanin can be appreciated in this biopsy specimen. A Fontana Masson would stain the melanin pigment black. There is also slightly increased dermal vascularity . (Right) Melanocytes are not increased in number but may be discernibly increased in size. Note the increased epidermal and dermal melanin . Note the mast cells  present.



## Large Melanocytes and Increased Melanin





## TERMINOLOGY

### Synonyms

- Mask of pregnancy
- Chloasma

### Definitions

- Pigmentary disorder characterized by symmetric hyperpigmented macules and patches typically on face

## ETIOLOGY/PATHOGENESIS

### Several Factors

- UV radiation, pregnancy, oral contraceptive medicine, drugs, genetic predisposition, thyroid disease

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Quite common, although exact incidence unknown
- Age
  - Average age is ~ 30 years for both men and women
- Sex
  - Much more common in women
  - Studies of M:F vary from 1:6 to up to 1:39 in some geographic regions
- Ethnicity
  - More common in darker skin types (Fitzpatrick types III, IV and V)

### Presentation

- Presents as brownish macules with irregular contours on sun-exposed areas
- 2 types
  - Centofacial
    - Lesions predominate in zygomatic, glabellar, frontal, nasal, upper lip, and chin areas
  - Peripheral
    - Preauricular, mandibular, and frontotemporal areas are affected
- In most studies, ~ 1/2 of cases are of centofacial type, and others are peripheral or mixed types
- In ~ 10% of cases, extrafacial melasma may also be present
  - Extrafacial lesions present as irregular, hyperchromic, symmetric skin discolorations
  - Arms, neck, sternal, and back are typical sites

### Treatment

- Most effective 1st-line treatment
  - Sun avoidance, sunscreen use, and triple therapy
    - Triple therapy consists of: Hydroquinone, tretinoin, and topical corticosteroids
- Chemical peels have moderate effect
- Lasers and light therapy have limited role (typically last resort)

### Prognosis

- Good
  - Lesions typically attenuate with proper treatment, prevention (sun avoidance), and with age

## MICROSCOPIC

### Histologic Features

- Diagnosis is usually made clinically, and histopathologic analysis is only rarely required
- Increased deposits of melanin in both epidermis and dermis (within dermal melanophages)
- Mild perivascular lymphohistiocytic infiltrate ± increased mast cells
- Vascularity in dermis is also increased
- Solar elastosis is usually discernible but does not differ from uninvolved skin
- Number of melanocytes is not increased
  - But melanocytes are enlarged and often show greater number of dendrites
- Biopsies of facial and extrafacial lesions show similar histopathology

## ANCILLARY TESTS

### Histochemistry

- Fontana-Masson may help highlight increased melanin in epidermis and dermis

### Dermoscopy

- Epidermal melasma shows diffuse reticular pigmentation of varying shades of brown that spares follicles
- Dermal melasma shows diffuse dark-brown to gray pseudoreticular pigmentation

### Wood Light Examination

- Lesions of melasma that are more intensely seen under Wood lamp respond better to topical treatments

### Melasma Area and Severity Index

- Clinical score used to quantify severity of facial melasma

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Solar lentigo (and other forms of lentigo)
  - Typically shows bud-like elongation of rete ridges with increased pigment at base of keratinocytic buds
  - Darker brown or black clinically and can occur on any sun-exposed site (typically on backs of hands)
- Postinflammatory hyperpigmentation
  - Majority of cases have clinical history of preceding inflammatory condition (most patients remember, some may not)
- Drug-induced hyperpigmentation
  - More common on extremities than face but can occur on face
  - More of steel-gray color clinically
- Ochronosis
  - Banana-shaped fibers in dermis that are brownish-yellow in color

## SELECTED REFERENCES

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2. Sanchez NP et al: Melasma: a clinical, light microscopic, ultrastructural, and immunofluorescence study. *J Am Acad Dermatol.* 4(6):698-710, 1981

# Idiopathic Guttate Hypomelanosis

## KEY FACTS

### TERMINOLOGY

- Synonym is leukoderma punctata

### ETIOLOGY/PATHOGENESIS

- Normal aging, repeated microtrauma, and actinic damage are linked to idiopathic guttate hypomelanosis

### CLINICAL ISSUES

- Hypopigmented macules that favor extremities of adults

### MICROSCOPIC

- Loss of epidermal melanin and reduced, but not absent, melanocytes

### ANCILLARY TESTS

- Fontana-Masson demonstrates reduced epidermal melanin
- MART-1, SOX10, or MITF show reduced, but not absent, melanocytes


### TOP DIFFERENTIAL DIAGNOSES

- Vitiligo
  - Decreased or absent epidermal melanin, absent melanocytes, and no skip areas of retained melanin
- Postinflammatory hypopigmentation
  - Normal complement of melanocytes and no skip areas of retained melanin
- Guttate lesions of lichen sclerosus
  - Should only cause confusion clinically

### DIAGNOSTIC CHECKLIST

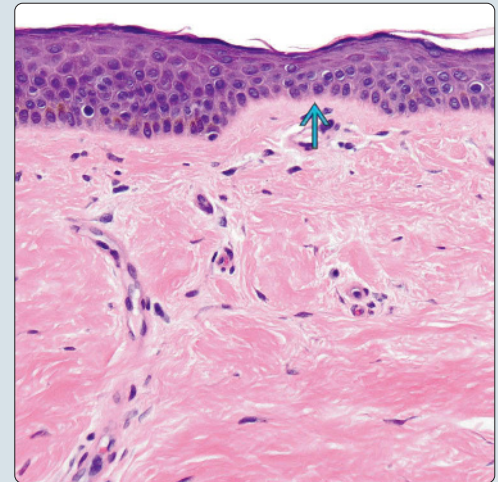
- Skip areas of retained melanin are seen in otherwise depigmented basal layer

**Hypopigmented Macules on Shins**



(Left) Idiopathic guttate hypomelanosis is shown with hypopigmented macules on the lower extremities of an elderly Asian adult. (Courtesy Y. Qureshi, MD.) (Right) Decreased melanization  is visible at high power.

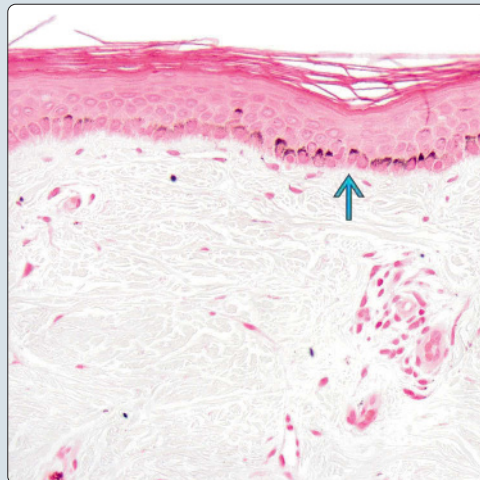


**Decreased Melanin in Epidermis**

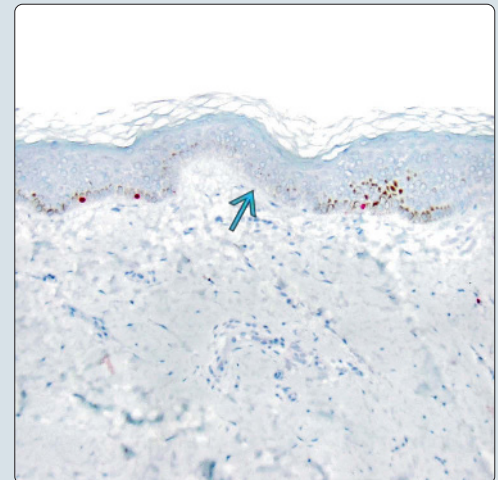


**Skip Areas of Retained Melanin**

(Left) Skip area of retained melanin  in a background of depigmentation is shown. This is a helpful clue to the diagnosis that can be readily appreciated with Fontana-Masson. (Right) Immunoperoxidase for SOX10 demonstrates decreased , but not absent, melanocytes at the dermoepidermal junction.



**Decreased Melanin and Decreased Melanocytes**





## TERMINOLOGY

### Abbreviations

- Idiopathic guttate hypomelanosis (IGH)

### Synonyms

- Leukoderma punctata

### Definitions

- IGH is common, benign leukoderma of unknown origin that is associated with sun exposure and aging

## ETIOLOGY/PATHOGENESIS

### Unclear

- Pathogenesis is unclear, but theories include normal aging, repeated microtrauma, and photodamage
  - However, based on statistical studies of age and skin type-matched cohorts, causal relationship between chronic actinic damage and IGH has not been established

## CLINICAL ISSUES

### Epidemiology

- Age
  - Based on study of clinical features in over 600 patients with IGH, average age is 53 years, but patients may develop lesions in their 20s

### Site

- Most common sites of involvement are distal lower and upper extremities
- Most patients have lesions on trunk as well, but face is only involved in 6% of patients

### Presentation

- Individual lesions are small achromic or hypopigmented macules that measure 0.2-1.5 cm in diameter
- Occasionally, patients may present with keratotic, flat-topped hypopigmented papules rather than macules
- No symptoms are associated

### Treatment

- Surgical approaches
  - Fractional carbon dioxide lasers have shown improvement in large number of patients following single treatment
  - Fractional photothermolysis with 1,550-nm ytterbium/erbium fiber laser has produced > 90% improvement in study of 120 lesions treated serially
  - In reports, 3- to 5-second cryotherapy and superficial dermabrasion have been successful
- Drugs
  - In controlled study, topical tacrolimus 0.1% ointment produced modest improvement (11%) after 6 months of treatment
  - Pimecrolimus 1% cream has also been reported to be useful

### Prognosis

- Lesions of IGH are harmless but persistent and may increase in number over time

## MICROSCOPIC

### Histologic Features

- Classic histologic findings include hyperkeratosis, epidermal atrophy with flattened retia, and decreased melanization with reduced number of melanocytes
  - However, in 1 study of 47 cases of IGH, hyperkeratosis was found in 40% of cases, but epidermal atrophy and flattened rete ridges were only present in 10% and 15%, respectively
  - Compared to perilesional skin, all cases show decreased epidermal melanin and reduced, but not absent, melanocytes, highlighted by Fontana-Masson and MART-1
  - Ultrastructurally, melanocytes in lesions of IGH show degeneration and reduced or absent melanosomes
- Perhaps most important and specific clue to diagnosis is presence of skip areas of retained melanin that are seen in otherwise depigmented basal layer
  - This finding is present in 80% of biopsies and is very useful in discrimination from vitiligo and postinflammatory hypopigmentation
  - While other 20% of cases show complete depigmentation akin to that seen in vitiligo
    - Melanocytes are not completely absent in IGH, as they are in established lesions of vitiligo
- In lesions that are more keratotic clinically, corresponding marked hyperkeratosis is present, with clear-cut margins distinguishable from adjacent normal epidermis

## ANCILLARY TESTS

### Histochemistry

- Fontana-Masson shows decreased epidermal melanin

### Immunohistochemistry

- MART-1, SOX10, and MITF
  - All 3 show reduced, but not absent, melanocytes and stain nucleus of melanocytes

## DIFFERENTIAL DIAGNOSIS

### Vitiligo (Particularly Guttate Lesions From Acral Surfaces)

- Decreased or absent epidermal melanin, absent melanocytes, and no skip areas of retained melanin

### Postinflammatory Hypopigmentation

- Normal complement of melanocytes and no skip areas of retained melanin

### Guttate Lesions of Lichen Sclerosus

- Should only cause confusion clinically

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Skip areas of retained melanin are seen in otherwise depigmented basal layer

## SELECTED REFERENCES

1. Joshi R: Skip areas of retained melanin: a clue to the histopathological diagnosis of idiopathic guttate hypomelanosis. *Indian J Dermatol.* 59(6):571-4, 2014

## KEY FACTS

### TERMINOLOGY

- Rare autosomal dominant pigmentary disorder characterized clinically by reticulate hyperpigmentation of flexures, comedone-like lesions, and pitted scars

### ETIOLOGY/PATHOGENESIS

- Autosomal dominant inheritance pattern caused by mutation in keratin 5 gene
  - Same mutation has been found in Galli-Galli disease suggesting that it is variant of Dowling-Degos disease (DDD)

### CLINICAL ISSUES

- Typically presents as acquired reticulated skin hyperpigmentation in flexural areas (armpits, groin) and later spreads to other skin folds (neck, inframammary/sternal areas)
  - Pigmentation presents as partly confluent central pigmented area with surrounding discrete, brownish black macules at periphery

- Galli-Galli disease clinically indistinguishable from DDD

### MICROSCOPIC

- Thinning of suprapapillary epidermis
- Antler- or finger-like elongation of rete ridges with basal layer hyperpigmentation
- Morphologically, resembles reticulated seborrheic keratosis
- Galli-galli has same histopathologic features but with
  - Suprabasal acantholysis and overlying parakeratosis ± dyskeratosis

### TOP DIFFERENTIAL DIAGNOSES

- Acanthosis nigricans
- Seborrheic keratosis
- Lentigo
- Confluent and reticulated papillomatosis of Gougerot and Carteaud

**Reticulate Brown Macular Hyperpigmentation**



*Axilla with light brown papules on the left and reticulate light brown macular hyperpigmentation on the right side of the figure are shown. Both of these types of hyperpigmentation in intertriginous areas are characteristic of Dowling-Degos disease.*



## TERMINOLOGY

### Abbreviations

- Dowling-Degos disease (DDD)

### Synonyms

- Reticulate pigmented anomaly
- Dark dot disease

### Definitions

- Rare autosomal dominant pigmentary disorder characterized clinically by reticulate hyperpigmentation of flexures, comedone-like lesions, and pitted scars

## ETIOLOGY/PATHOGENESIS

### Inherited Mutation

- Autosomal dominant inheritance pattern caused by mutation in keratin 5 gene
  - Loss of function mutation
  - Variable penetrance clinically
  - Same mutation has been found in Galli-Galli disease, suggesting that it is variant of DDD

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Rare
  - True prevalence is unknown
- Age
  - Usually presents in 3rd-4th decades of life
    - i.e., at puberty or in early adolescence
- Sex
  - Appears to be slight female predominance
    - Some articles report no sex predilection
    - Others report M:F = 1:2
- Ethnicity
  - No predilection

### Site

- Typically begins in axillae and groin (flexural areas) and later in life spreads to other skin folds
  - Can also uncommonly spread to antecubital and popliteal fossae, wrists, scalp, face, scrotum, and vulva

### Presentation

- Numerous clinical patterns have been described
  - Typically presents as acquired reticulated skin hyperpigmentation in flexural areas (armpits, groin) and later spreads to other skin folds (neck, inframammary/sternal areas)
    - Pigmentation presents as partly confluent central pigmented area with surrounding discrete, brownish black macules at periphery
  - Comedo-type lesions can occur in some patients on back and neck
  - Cribiform scars and perioral acne (sometimes pigmented) can occur in some patients as well
  - Follicular papules may be present
  - Reduced pigmentation may be present
    - Pale macular or papular areas may be seen
- Itchiness may or may not be present

- Condition may worsen during hot weather
- Epidermoid cysts may also be present
- Hidradenitis suppurativa-like lesion can occur in axillae or groin
  - Patients with DDD are actually more likely to have hidradenitis suppurativa
- Galli-Galli disease (variant of classic DDD)
  - Clinically indistinguishable from classic DDD
    - Only difference is presence of acantholysis histopathologically

### Treatment

- Options, risks, complications
  - Variety of treatments have been tried all with limited success
  - Successful treatment with Er:YAG laser was reported in 1 patient
- Drugs
  - Topical steroids may relieve some of itchiness

## MICROSCOPIC

### Histologic Features

- 2 histopathologic variants
  - Classic
    - Ortho- or hyperkeratosis
    - Thinning of suprapapillary epidermis
    - Antler- or finger-like elongation of rete ridges with basal layer hyperpigmentation
      - ◻ Morphologically resembles reticulated seborrheic keratosis
    - Comedones may be present
    - Dermal melanophages
    - Perivascular lymphohistiocytic infiltrate
  - Galli-Galli
    - Same histopathologic features as in classic DDD but with
      - ◻ Suprabasal acantholysis and overlying parakeratosis
      - ◻ ± dyskeratosis

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Acanthosis nigricans
  - Less pronounced elongation of rete ridges
  - No comedones
  - Clinically, demonstrates velvety plaques without follicular involvement
- Seborrheic keratosis
  - Specifically reticulated pattern of seborrheic keratosis
    - Can be appear very similar to reticulated seborrheic keratosis
    - No comedones histopathologically
    - Clinically more discrete lesions and usually more widespread (i.e., not limited to flexural areas)
      - ◻ No cribriform scars, perioral acne, or comedo-type lesions
      - ◻ Not reticulated clinically
- Lentigo
  - In solar lentigines, can have elongation of rete ridges but more uniform

- Solar elastosis is present underlying
  - o No dermal melanophages and typically no lymphohistiocytic infiltrate
  - o No comedones
  - o Clinically on sun-exposed sites
- Confluent and reticulated papillomatosis of Gougerot and Carteaud
  - o Subtle papillomatosis with more mild acanthosis (not antler- or finger-like)
  - o Mild basal layer hyperpigmentation may be present
  - o Clinically, asymptomatic red to brown papules that become confluent with peripheral reticulate pattern
    - Upper chest and back most commonly affected
    - Not as pigmented clinically as DDD
- Tumor of follicular infundibulum
  - o Plate-like growth of anastomosing strands that run parallel to epidermis and show follicular differentiation
    - Peripheral palisading of basaloid cells
  - o Uniform pigmentation at base is not seen
  - o Clinically, usually solitary lesion
    - Occasionally can be eruptive (sudden onset of multiple lesions)
- Pigmented actinic keratosis
  - o Cytologic atypia along basal layer
  - o Typically underlying solar elastosis
  - o Arise on chronically sun-exposed sites clinically
- Grover disease (GD)
  - o Mainly just for acantholytic variant of DDD (Galli-Galli disease)
    - Lentiginous elongation of rete ridges is not seen in GD
    - Histopathologically, can show several patterns (Hailey-Hailey-like, Grover-like, pemphigus vulgaris-like, and pemphigus foliaceus-like)
    - Spongiosis and eosinophils typically present
  - o Clinically, presents as sudden eruption of small red pruritic papules typically on trunk of middle-aged or elderly men
    - Brown, lentigo-like lesions are not seen clinically
    - No predilection for flexural areas clinically
- No antler-like elongation
- Darier disease
  - o Very perifollicular and keratotic (feels rough clinically)
  - o When confluent, becomes yellowish-greasy plaque
  - o Not reticulate
  - o Chest and upper back are typical clinical locations
- Epidermal nevus
  - o Linear, usually unilateral
    - Can become generalized (very rare)
  - o Not reticulate clinically
  - o Clinically, can occur at any location (no predilection for axillae or groin)
  - o Asymptomatic
- Scleroderma
  - o Can get macular-brownish pigmentation in one stage of scleroderma
    - Usually it evolves from lilac pink color 1st
    - Ultimately becomes porcelain-white and indurated
  - o Induration may be present
  - o Not reticulate clinically
- Epidermolysis bullosa simplex with mottled pigmentation
  - o Histopathologically, shows splitting between basal keratinocytes with focal basilar hyperpigmentation and pigment incontinence
    - No lymphohistiocytic infiltrate, no elongation of rete ridges
    - Molecular testing (DNA mutation analysis), immunofluorescent microscopy, and electron microscopy are typically necessary to definitively diagnose
  - o Clinically has mottled pigmentation of extremities and trunk
    - Onset is usually at birth or infancy
    - Intraepidermal blisters occur with minimal trauma, nail dystrophy, and hyperkeratotic papules on extensor surfaces
  - o Also due to mutation in keratin 5 gene (missense mutation)
  - o Extremely rare variant of very rare disease

## Clinical

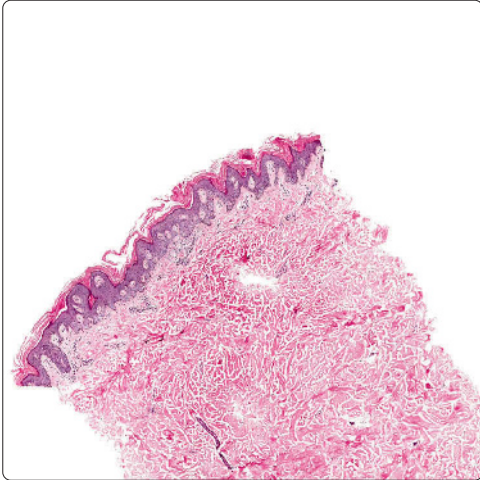
- Acanthosis nigricans
  - o Velvety feel clinically
  - o Asymptomatic
  - o More of confluent area clinically (not reticulated)
  - o Also flexural (like DDD)
- Ephelides
  - o Only sun-exposed areas (sun-induced)
  - o Discrete pigmented macules
- Confluent and reticulated papillomatosis of Gougerot and Carteaud
  - o Clinically, usually appears on upper trunk (back and chest) 1st and then can spread gradually to neck, axillae, and abdomen
  - o Not as much pigment clinically
  - o Asymptomatic (not itchy)
- Axillary freckles in neurofibromatosis type 1
  - o Patients can often get lentigines in axillae and groin
  - o Well-demarcated, individual lesions
  - o Demonstrate lentigo on biopsy

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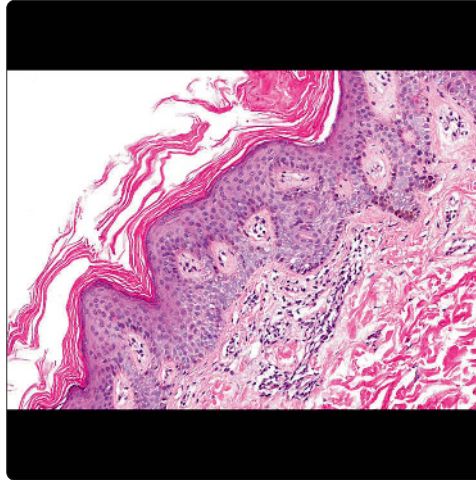
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**Hyperkeratosis, Mild Acanthosis, and Basilar Hyperpigmentation**

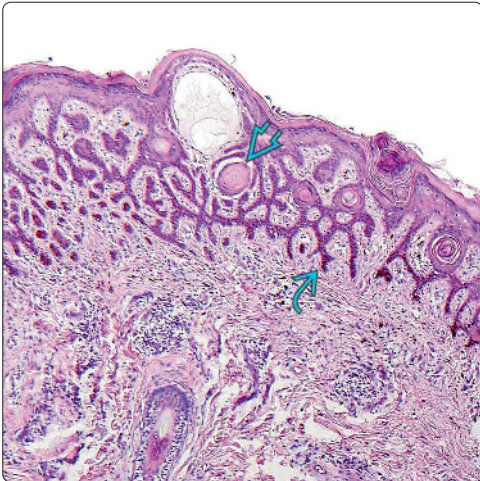


**Hyperkeratosis, Rete Ridge Elongation, and Basilar Hyperpigmentation**

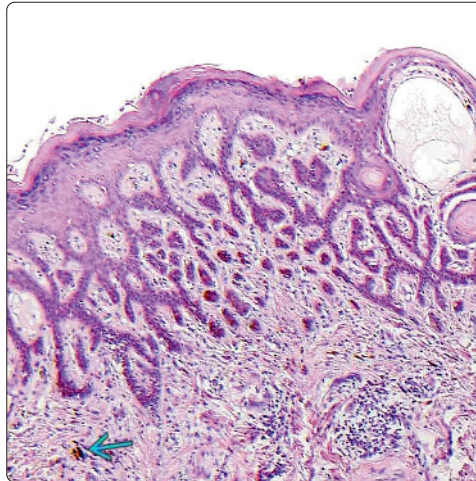


(Left) With slight acanthosis, basal hyperpigmentation, and hyperkeratosis, from low power, the differential diagnosis of Dowling-Degos disease would include acanthosis nigricans, confluent and reticulated papillomatosis, and seborrheic keratosis. (Right) There is slight rete ridge elongation, basal layer hyperpigmentation, and hyperkeratosis with suprapapillary plate thinning.

**Antler-Like Elongation of Rete Ridges**



**Finger-Like Rete Ridge Elongation**



(Left) The rete ridge elongation (acanthosis) has sometimes been described as antler- or finger-like. Comedones and a perivascular lymphohistiocytic infiltrate can be seen. (Right) Finger- or antler-like rete ridge elongation with basal layer hyperpigmentation, dermal melanophages, and occasional comedones is shown.

**Rete Ridge Elongation and Focal Acantholysis**



**Suprabasilar Acantholysis in Galli-Galli**



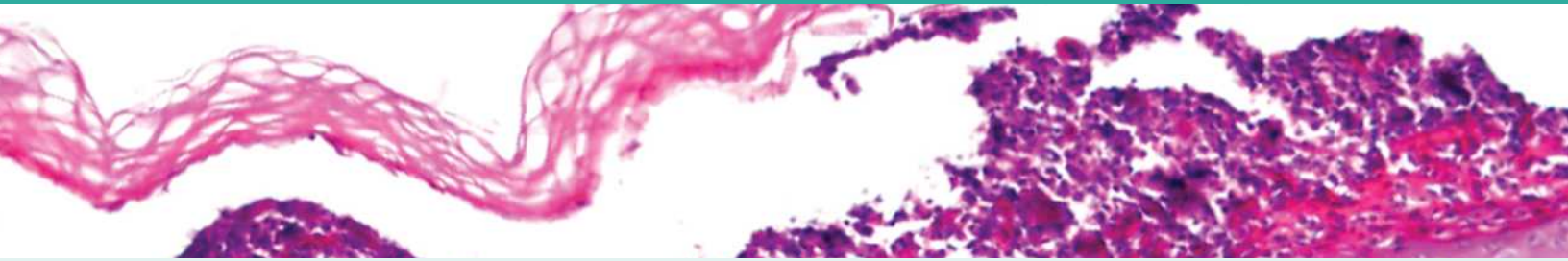
(Left) Galli-Galli disease also shows basilar hyperpigmentation, mild acanthosis, hyperkeratosis and suprapapillary thinning. Acantholysis is the only distinguishing feature. (Right) Often there is parakeratosis above the area of acantholysis in Galli-Galli. A superficial lymphohistiocytic infiltrate, and other features of Dowling-Degos, are also present.

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## SECTION 16

# Neutrophilic Dermatoses



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## Sweet Syndrome

## KEY FACTS

## ETIOLOGY/PATHOGENESIS

- Paraneoplastic Sweet syndrome (SS)
  - Clinical symptoms and histology indistinguishable from classical SS
  - Underlying hematologic or solid malignancy may be associated with ~ 25% of cases
- Drug-induced SS
  - Clinical symptoms and histology indistinguishable from "classical" SS
  - Usually temporal relationship between drug administration and symptom onset
- Neutrophilic dermatosis of dorsal hands
  - Probably represents localized, pustular variant of SS
  - As name implies, lesions are limited to dorsal hands and show pustules, ulcerated nodules or plaques

## CLINICAL ISSUES

- Abrupt onset of fever, malaise, and neutrophilic leukocytosis

- Asymmetrical, often bilateral, tender, painful nodules, pustules or plaques affecting neck, face, and extremities

## MICROSCOPIC

- Hallmark is intense dermal infiltrate of mononuclear cells (especially neutrophils) often sparing epidermis
- Polymorphous inflammatory infiltrate (including eosinophils, lymphocytes, plasma cells, histiocytes) can infiltrate entire dermis, even into subcutis
- Epidermal spongiosis, vesiculation or pustules
- Leukocytoclasia is very common
- Often marked edema of papillary dermis
- **Histiocytoid variant** demonstrates numerous immature histiocyte-like myeloid cells (not true histiocytes)

## TOP DIFFERENTIAL DIAGNOSES

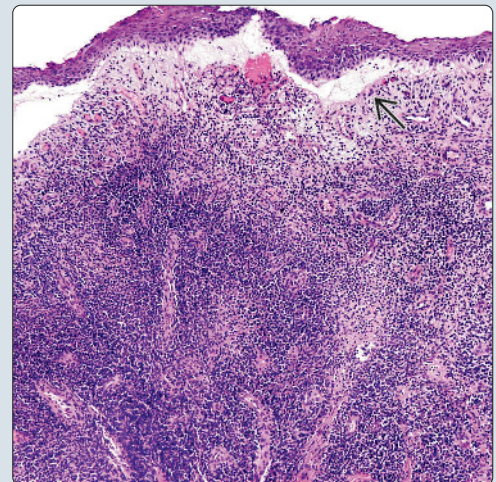
- Early erythema elevatum diutinum
- Granuloma faciale
- Pyoderma gangrenosum

Purple-Red Plaque With Fever

(Left) Sweet syndrome on the lower leg shows a purple-red plaque [A]. Clinically, one expects fever and rapid response to systemic corticosteroids. Underlying disease, especially leukemia, should be considered. (Right) Low-power view of Sweet syndrome shows a dense dermal inflammatory infiltrate that almost obscures the dermis. Note also the marked edema of the papillary dermis [B].

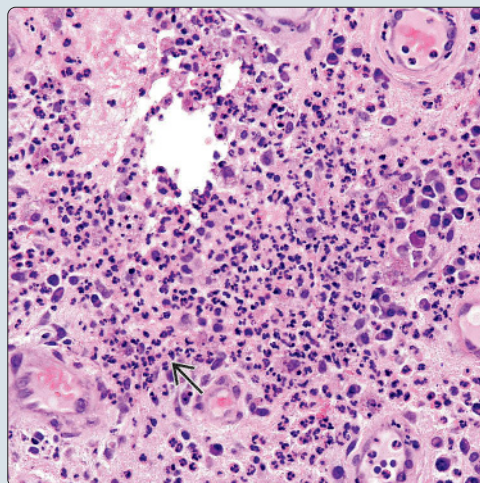


Dense Dermal Neutrophilic Infiltrate With Papillary Edema

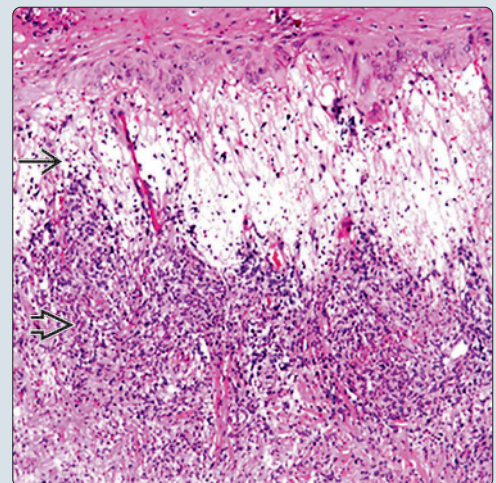


Numerous Dermal Neutrophils

(Left) Another view of Sweet syndrome demonstrates numerous neutrophils [C] that are perivascular and diffuse. (Right) Another case of Sweet syndrome demonstrates more obvious subepidermal edema [D] overlying a dense neutrophilic inflammatory infiltrate in the dermis [E].



Subepidermal Edema and Dense Neutrophilic Infiltrate





**TERMINOLOGY****Abbreviations**

- Sweet syndrome (SS)

**Synonyms**

- Acute neutrophilic dermatosis of Sweet, acute febrile neutrophilic dermatosis, Sweet, Gomm-Button disease

**Definitions**

- Neutrophilic dermatosis characterized by
  - Abrupt onset of fever, malaise, and neutrophilic leukocytosis
  - Asymmetrical, often bilateral, tender, painful nodules or red plaques affecting neck, face, and extremities

**ETIOLOGY/PATHOGENESIS****Unknown**

- Presumed to be sort of hypersensitivity reaction

**Paraneoplastic Sweet Syndrome**

- Clinical symptoms and histology indistinguishable from classical Sweet syndrome
- Underlying hematologic or solid malignancy may be associated with approximately 25% of cases
  - Acute myelogenous leukemia and solid tumors of GU, GI, or breast are most commonly associated
- May precede, be concurrent with, or follow diagnosis of malignancy
  - May also be marker of recurrent malignancy in patients with previous cancer diagnoses

**Drug-Induced Sweet Syndrome**

- Clinical symptoms and histology indistinguishable from "classical" Sweet syndrome
- Usually temporal relationship between drug administration and symptom onset
- Should be temporal resolution of symptoms upon withdrawal or treatment with systemic corticosteroids
- Most common drug responsible is granulocyte colony-stimulating factor, but others also implicated

**Neutrophilic Dermatitis of Dorsal Hands**

- Also referred to as pustular vasculitis of dorsal hands
- Probably represents localized, pustular variant of SS
- As name implies, lesions are limited to dorsal hands and show pustules, ulcerated nodules or plaques
- Histology is indistinguishable from SS

**CLINICAL ISSUES****Epidemiology**

- Age
  - Most common in 3rd-6th decades of life
- Sex
  - Predominantly affects women (M:F ~ 1:5)

**Presentation**

- Fever
- Raised, painful, and tender erythematous papules, nodules or plaques on neck, face, and limbs
- Polymorphonuclear lymphocytosis
- Often preceded by upper respiratory infection

**Treatment**

- Systemic corticosteroids or potassium iodide generally show excellent response
  - However, recurrences are common and often prove more difficult to treat

**Prognosis**

- Generally good except for paraneoplastic SS

**MICROSCOPIC****Histologic Features**

- Hallmark is intense dermal infiltrate of mononuclear cells (especially neutrophils) often sparing epidermis
  - Polymorphous inflammatory infiltrate (including eosinophils, lymphocytes, plasma cells, histiocytes) can infiltrate entire dermis, even into subcutis
  - Dense neutrophils may simulate abscess
  - Epidermal spongiosis, vesiculation or pustules
- Leukocytoclasia is very common
- Rare, neutrophil-poor form has been reported
- Endothelial swelling may be present, but not vasculitis
  - No vessel wall necrosis
- Often marked edema of papillary dermis
- Extravasated erythrocytes may be present
- **Histiocytoid variant** demonstrates numerous immature histiocyte-like myeloid cells (not true histiocytes)
  - Cells are myeloperoxidase (MPO) positive
- In some patients with myelodysplasia or leukemia, rare **lymphocytic variant** has been described
  - More classic histology of neutrophilic SS may occur months or years later

**ANCILLARY TESTS****Histochemistry**

- Gram or PAS stain should be performed to rule out infectious etiology

**DIFFERENTIAL DIAGNOSIS****Histopathologic**

- **Pyoderma gangrenosum**
  - Characteristic ulcers with rolled edges that differ from painful erythematous plaques of SS
  - Often less karyorrhexis than SS, however histologic findings in pyoderma gangrenosum are nonspecific
- **Erythema elevatum diutinum**
  - Early lesions indistinguishable from SS
  - Late lesions show fibrosis
- **Granuloma faciale**
  - Grenz zone and eosinophils often prominent

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# Pyoderma Gangrenosum

## KEY FACTS

### CLINICAL ISSUES

- Ulcerative lesions have clinically distinct undermined or rolled edges with red to violaceous border
- Surgery is contraindicated due to pathergy, and accurate diagnosis is critical
- ~ 1/2 of patients have associated underlying disease
- Most common disease association is inflammatory bowel disease

### MICROSCOPIC

- Earliest lesion is folliculitis
- Developed lesions show necrotic or ulcerated epidermis with pustules at advancing edge
  - Deep ulcer is typically present in middle of lesion
    - With diffuse infiltrate of neutrophils, lymphocytes, and histiocytes at base
  - At edge (margin) of lesion there is typically lymphocytic or neutrophilic vasculitis

- Typically lymphocytic cuffing of vessels (thought to be secondary vasculitic process)
- Often subepidermal edema
- Sometimes pseudoepitheliomatous hyperplasia and acanthosis

### ANCILLARY TESTS

- Culture is required to rule out infection clinically

### TOP DIFFERENTIAL DIAGNOSES

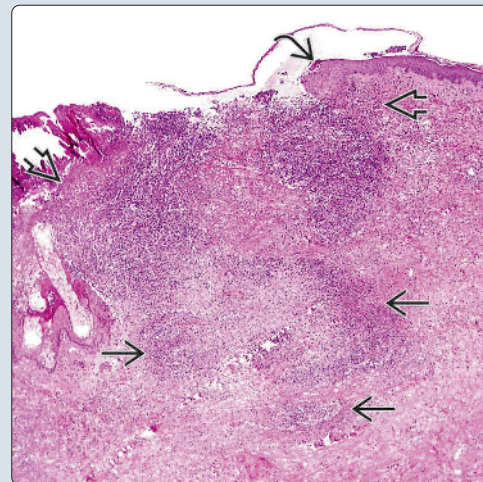
- Histologic differential diagnosis
  - Granulomatosis with polyangiitis (Wegener)
  - Sweet syndrome
  - Bite reaction
  - Factitial ulcer
  - Deep infection or necrotizing fasciitis

Ulcer With Rolled Border Appearance

(Left) *Pyoderma gangrenosum* (PG) demonstrates ulceration with undermining of the remaining intact epidermis, giving it the characteristic rolled border appearance. (Right) Low-power view of PG shows a deep ulcer with a neutrophilic infiltrate at the edges, undermining the remaining intact epidermis.

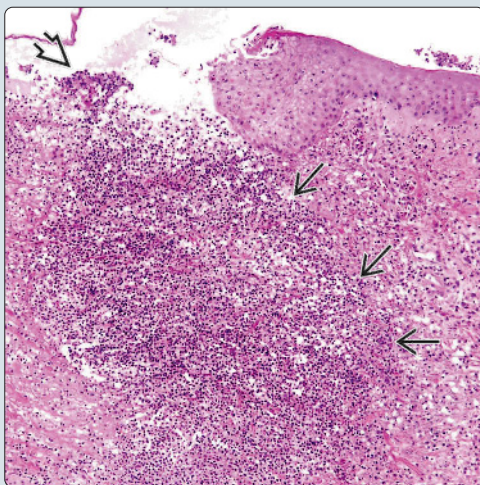


Ulcer With Neutrophilic Infiltrate and Undermining of Epidermis



Ulcer With Undermining of Epidermis, High Power

(Left) The edge of PG demonstrates undermining of the epidermis by numerous neutrophils and epidermal ulceration. (Right) Early PG shows a lack of epidermal ulceration but the same characteristic deep dermal ulcer with hemorrhage and numerous neutrophils.



Early Lesion With Diffuse Neutrophilic Infiltrate and Hemorrhage





## TERMINOLOGY

### Abbreviations

- Pyoderma gangrenosum (PG)

### Definitions

- Uncommon ulcerative, cutaneous condition of unknown etiology that begins as erythematous pustule or nodule
  - Rapidly progresses to necrotic ulcer with distinctive undermined or rolled edges and violaceous border
    - Commonly associated with systemic disease

## ETIOLOGY/PATHOGENESIS

### Disease Associations

- ~ 1/2 of patients will have associated underlying disease
- Most common disease association is inflammatory bowel disease (IBD)
  - Both Crohn and ulcerative colitis patients can develop PG
  - Successful treatment of underlying IBD can lead to complete remission of PG
- HIV, hepatitis C, SLE, rheumatoid arthritis, leukemia, monoclonal gammopathy, myeloma, pregnancy, Takayasu arteritis, and others

## CLINICAL ISSUES

### Epidemiology

- Age
  - Most common in 5th and 6th decades
  - Uncommon in children

### Site

- Most commonly occurs on trunk and lower extremities but can occur anywhere

### Presentation

- Clinically divided into 4 different types
  - Ulcerative or classic, bullous, vegetative, and pustular
- Ulcerative lesions have clinically distinct undermined or rolled edges with red to violaceous border
- Lesions often occur at sites of trauma (pathergy)
- Heals with characteristic atrophic, thin scars

### Treatment

- Drugs
  - Adalimumab has shown promising results recently
  - Prednisolone usually 1 of initial drugs in therapy
    - Large randomized study demonstrated no difference in efficacy vs. cyclosporine
  - Dapsone, mycophenolic acid (CellCept), cyclosporine have been used in combination with steroids
  - Better treatments urgently needed
- Difficult and depends on type of lesion and whether there is associated underlying disease
- Surgery is contraindicated due to pathergy; accurate diagnosis is critical

## MICROSCOPIC

### Histologic Features

- Findings may be entirely nonspecific
- Earliest lesion is folliculitis

- Resembles neutrophilic dermatosis
- Vasculitis sometimes present
- Developed lesions show necrotic or ulcerated epidermis with pustules at advancing edge
  - Deep ulcer is typically present in middle
    - With diffuse infiltrate of neutrophils, lymphocytes, and histiocytes at base
    - Associated abscess formation is common
  - At edge (margin) of lesion
    - Typically lymphocytic cuffing of vessels (thought to be secondary vasculitic process)
      - ◻ Sometimes vasculitis is predominately neutrophilic
      - ◻ Vessel involvement reportedly can range from nonexistent to fibrinoid necrosis
    - Often subepidermal edema
    - Sometimes pseudoepitheliomatous hyperplasia and acanthosis
- Presence of giant cells may be supportive of IBD as underlying cause

## ANCILLARY TESTS

### Culture

- Required to rule out infection clinically

## DIFFERENTIAL DIAGNOSIS

### Histologic Differential Diagnosis

- **Granulomatosis with polyangiitis (Wegener)**
  - PG-like clinical lesions of face can be seen in Wegener
  - Histology differs from classic PG and instead shows
    - Foci of palisaded neutrophilic and granulomatous dermatitis
    - Prominent granulomatous and neutrophilic necrotizing vasculitis
    - Basophilic collagen degeneration
- **Sweet syndrome**
  - Typically not associated with ulceration
  - More prominent karyorrhexis and papillary edema
  - Inflammatory infiltrate is often deeper and more extensive in PG
- **Bite reaction**
  - Clinically evolves more quickly and can be associated with other systemic findings
  - Usually wedge-shaped with numerous eosinophils
- **Factitial ulcer**
  - Clinical history is necessary to differentiate from PG
- **Deep infection or necrotizing fasciitis (NF)**
  - Typically involves deeper subcutaneous and facial tissue
    - PG mostly affects dermis, with rarer subcutaneous involvement
  - NF shows sheets of bacteria or fungi in deep tissue

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## Subcorneal Pustular Dermatitis

## KEY FACTS

## TERMINOLOGY

- Uncommon chronic, relapsing, sterile, symmetric vesiculopustular dermatosis that typically involves flexural upper extremities and trunk

## CLINICAL ISSUES

- Classically affects women in their 40s and 50s
- Classic "half and half" blisters with clear fluid overlying sterile pus
- Most cases rapidly respond to oral dapsone

## MICROSCOPIC

- Normal epidermis with minimal spongiosis, no acantholysis, and subcorneal pustules filled with neutrophils

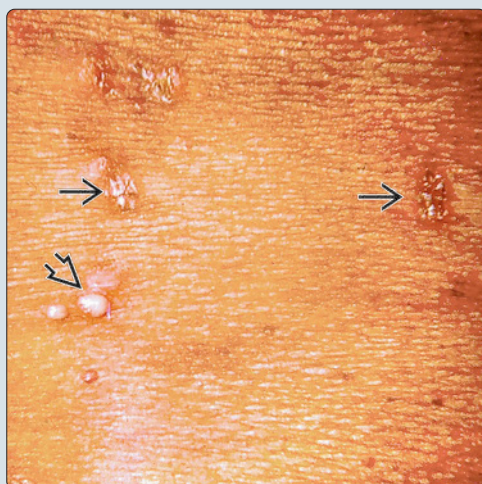
## TOP DIFFERENTIAL DIAGNOSES

- Pustular psoriasis
  - Spongiotic epidermis with diffuse Munro microabscesses and spongiform pustules
- Acute generalized exanthematous pustulosis

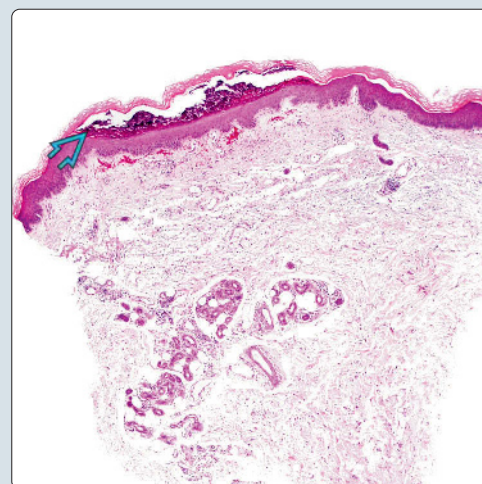
- Rapidly developing sterile pustules associated with fever and leukocytosis in response to drug ingestion
- Pemphigus foliaceus
  - Subcorneal blister filled with eosinophils, neutrophils, and acantholytic, dyskeratotic, hyperchromatic keratinocytes in granular cell layer
  - Direct immunofluorescent (DIF) demonstrates intercellular IgG and C3
- Bullous impetigo
  - Subepidermal bulla with neutrophils and acantholysis in granular layer; gram (+) cocci usually demonstrable
- Dermatitis herpetiformis
  - Extremely pruritic vesiculobullous disease affecting extensor surfaces (vs. flexural in subcorneal pustular dermatosis) such as knees, elbows, and buttocks
  - Neutrophilic abscesses at tips of dermal papillae with subepidermal vesicles
  - DIF demonstrates granular IgA deposits at tips of dermal papillae

Intact and Ruptured Pustules

(Left) Subcorneal pustular dermatosis is shown with intact [E] and ruptured [E] pustules. (Right) Low-power view of subcorneal pustular dermatosis (SPD) demonstrates a subcorneal blister filled with neutrophils [E]. There is sparse inflammation in the dermis, along with mild epidermal acanthosis.

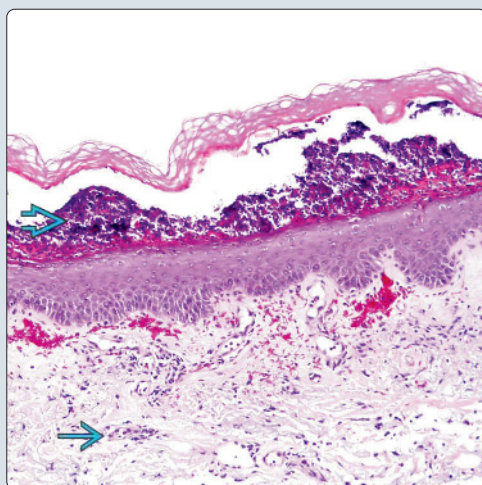


Subcorneal Blister With Neutrophils

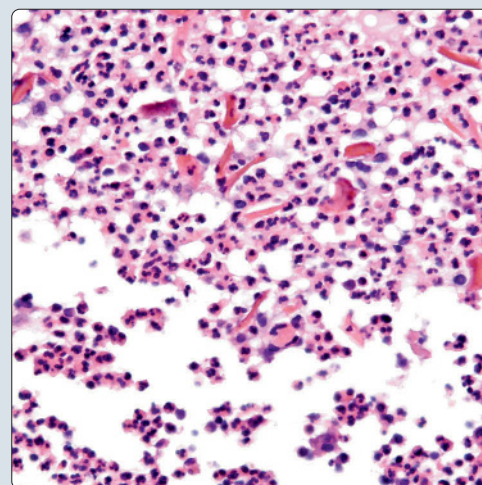


Subcorneal Blister With a Base of Neutrophils

(Left) Higher power view of SPD demonstrates a mild perivascular infiltrate [E], a subcorneal blister filled with a base of neutrophils [E] and occasional eosinophils, and a normal epidermis. (Right) Neutrophils are the predominant constituent of the subcorneal blister. Rare eosinophils may be admixed.



Neutrophils in Subcorneal Pustule





## TERMINOLOGY

### Abbreviations

- Subcorneal pustular dermatosis (SPD)

### Synonyms

- Sneddon-Wilkinson disease (SWD)
  - Subcorneal type of IgA pemphigus (some consider this subtype of SWD, some consider it subgroup of pemphigus)
  - Similar histologic and clinical findings as SPD

### Definitions

- Uncommon chronic, relapsing, sterile, symmetric, vesiculopustular dermatosis that typically involves flexural upper extremities and trunk

## ETIOLOGY/PATHOGENESIS

### Unknown

- However, associated with several diseases including
  - Lymphoproliferative disorders, Crohn disease, monoclonal gammopathy, multiple myeloma, RA, pyoderma gangrenosum, others
  - Screening of patients for lymphoproliferative disorder is warranted
  - Autoimmune disorders are most frequently encountered

## CLINICAL ISSUES

### Epidemiology

- Sex
  - Classically affects women in their 40s and 50s

### Presentation

- Waves of isolated or grouped flaccid pustules 2-4 mm in diameter that appear on normal or erythematous skin
- Lesions may evolve into classic "half and half" blisters with clear fluid in upper 1/2 and sterile pus in lower 1/2
  - Pustules may coalesce to form annular, serpiginous, or circinate patterns
  - Pustules easily rupture upon contact
- Classically, eruption is symmetric and involves trunk, intertriginous areas, and flexor areas of extremities
  - Face and mucous membranes almost never affected; rare reports of palmar or sole involvement
- Mild hyperpigmentation may ensue when eruption resolves

### Treatment

- Drugs
  - Most cases rapidly respond to oral dapsone (response to dapsone helps solidify diagnosis)
  - Alternatives include: Acitretin, sulfapyridine, sulfamethoxypyridazine, PUVA, broad- or narrow-band UVB, and corticosteroids
- In cases associated with underlying malignancy, successful treatment of malignancy usually also improves SPD

### Prognosis

- Normally good, except for cases associated with lymphoproliferative disorder

## MICROSCOPIC

### Histologic Features

- Normal epidermis with minimal to no spongiosis and usually no acantholysis (rare acantholytic cells seen in some older lesions)
- Early lesions show perivascular inflammation with neutrophils and occasional eosinophils
- Lesions progress to subcorneal pustules filled with neutrophils and often occasional eosinophils

## ANCILLARY TESTS

### Immunofluorescence

- Indirect and direct immunofluorescent (DIF) studies typically negative
- Subcorneal type of IgA pemphigus: DIF shows intercellular IgA deposits directed against desmocollin 1
  - Deposits may not appear until years after diagnosis (repeat immunofluorescent studies may be indicated)

## DIFFERENTIAL DIAGNOSIS

### Pustular Psoriasis

- Spongiotic epidermis with diffuse Munro microabscesses and spongiform pustules

### Acute Generalized Exanthematous Pustulosis

- Rapidly developing sterile pustules associated with fever and leukocytosis in response to drug ingestion
- Subcorneal neutrophilic pustules commonly with eosinophils, rarely scattered apoptotic keratinocytes, and overlying parakeratosis

### Pemphigus Foliaceus

- Subcorneal blister filled with eosinophils, neutrophils, and acantholytic, dyskeratotic, hyperchromatic keratinocytes in granular cell layer
- DIF demonstrates intercellular IgG and C3

### Bullous Impetigo

- Subepidermal bulla with neutrophils and acantholysis in granular layer
- Gram (+) cocci usually demonstrable

### Dermatitis Herpetiformis

- Extremely pruritic vesiculobullous disease affecting extensor surfaces (vs. flexural in SPD) such as knees, elbows, and buttocks
- Neutrophilic abscesses at tips of dermal papillae with subepidermal vesicles
- DIF demonstrates granular IgA deposits at tips of dermal papillae

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## Neutrophilic Eccrine Hidradenitis

## KEY FACTS

## TERMINOLOGY

- Neutrophilic infiltration and destruction of eccrine glands

## ETIOLOGY/PATHOGENESIS

- Usually associated with induction chemotherapy
- Has been reported in other patients with malignancies, HIV, Behçet disease, and bacterial infections

## CLINICAL ISSUES

- Age
  - Has been reported in all age groups
- Sex
  - Slight male predominance
- Multiple plaques &/or nodules, usually on trunk
- Erythema, ± pruritus, may mimic cellulitis
- Resolves within a few weeks



## MICROSCOPIC

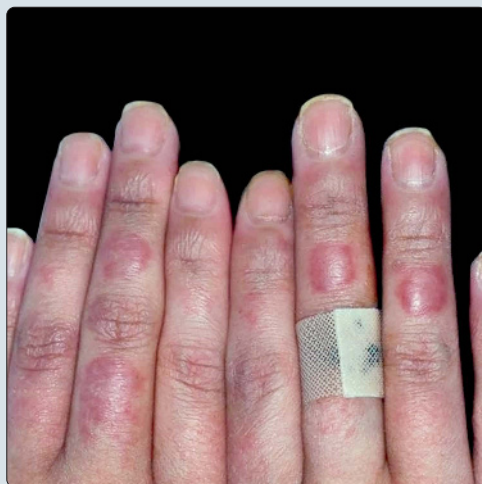
- Dense neutrophilic infiltrate localized to eccrine glandular apparatus
- Subsequent necrosis and prominent vacuolar change along basement membrane surrounding eccrine glands
- Reactive changes: Cellular atypia, squamous metaplasia, edema, mucin deposition
- Usually no overlying epidermal involvement

## TOP DIFFERENTIAL DIAGNOSES

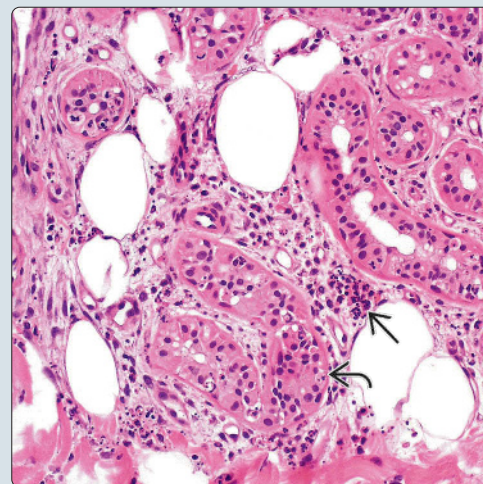
- Cellulitis
- Sweet syndrome (acute febrile neutrophilic dermatosis)
- Pyoderma gangrenosum
- Palmoplantar eccrine hidradenitis
- Abscess
- Erythema multiforme
- Erythema nodosum
- Drug eruptions
- Urticarial vasculitis

Erythematous Papules

(Left) Erythematous bullae appeared clinically over the dorsal fingers of this patient on chemotherapy. Biopsy showed neutrophilic eccrine hidradenitis. (Right) Neutrophils can be seen infiltrating into  and in between  these eccrine glands. (Courtesy S. Billings, MD.)

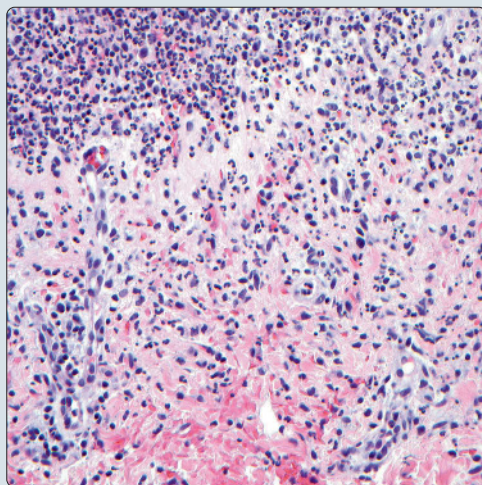


Neutrophils Around Eccrine Glands

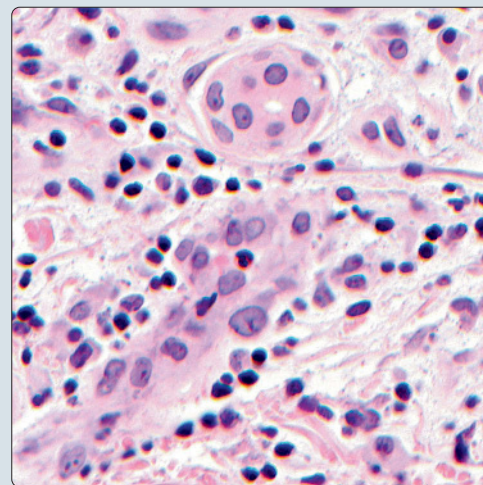


Cellulitis With Diffuse Dermal Infiltrate

(Left) Cellulitis may involve the eccrine glands, but there is a diffuse dermal mixed infiltrate. (Right) Other disorders can have inflammatory involvement of the eccrine glands. In abscesses, there is typically a mixed inflammatory infiltrate.



Mixed Infiltrate in Other Disorders





## TERMINOLOGY

### Abbreviations

- Neutrophilic eccrine hidradenitis (NEH)

### Synonyms

- Toxic erythema of chemotherapy

### Definitions

- Neutrophilic infiltration and destruction of eccrine glands

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- Generally not attributed to chemotherapy
- Patients with malignancies, HIV, and Behçet disease
- Infectious agents like *Serratia marcescens*, *Nocardia asteroides*, *Streptococcus* species, *Staphylococcus* species, *Enterobacter* species, *Pseudomonas* species

### Complication of Induction Chemotherapy

- Cytarabine, bleomycin, methotrexate, cyclophosphamide, granulocyte colony-stimulating factor, other chemotherapeutic agents

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Unknown
- Age
  - Has been reported in all age groups
- Sex
  - Slight male predominance

### Site

- Usually trunk

### Presentation

- Multiple plaques &/or nodules
- Erythema
  - May mimic cellulitis
- ± pruritus, pain/tenderness
- Resolves within a few weeks

## MICROSCOPIC

### Histologic Features

- Dense neutrophilic infiltrate localized to eccrine glandular apparatus
- Subsequent necrosis and prominent vacuolar change along basement membrane surrounding eccrine glands
- Reactive changes
  - Cellular atypia, squamous metaplasia, edema, mucin deposition
- Usually no overlying epidermal involvement
  - Lichenoid infiltrates have been reported

## DIFFERENTIAL DIAGNOSIS

### Histological

- Cellulitis
  - Infectious etiology
  - Necrosis may be present

- Deep pyogenic infection: May involve subcutis
- Diffuse infiltration by neutrophils without abscesses
- Sweet syndrome (acute febrile neutrophilic dermatosis)
  - Fever with painful erythematous papules, plaques, and nodules
  - Typically arises on face and extremities
  - Superficial dermal edema and dense diffuse neutrophilic infiltration of dermis
    - No abscess formation
  - No vasculitis
- Pyoderma gangrenosum
  - Single erythematous nodule or pustule
  - Progresses to necrotic, ulcerated lesion
  - Most cases have leukocytoclastic vasculitis
  - Mixed inflammatory infiltrate with abscess formation
  - Acanthosis, edema, and superficial perivascular lymphocytes and plasma cells at advancing edge
- Palmoplantar eccrine hidradenitis
  - Presents in children
  - Erythematous nodules only on palms &/or soles
  - No squamous metaplasia
  - Exposure to wet and cold environments has been proposed as causative
    - Seasonal variation noted consistent with this
  - Resolves spontaneously in 2-4 weeks
- Abscess
  - Dense neutrophil aggregates
  - Does not exclusively involve eccrine units

### Clinical

- Erythema multiforme
  - May have fever, skin lesions, lesions of oral mucosa (Stevens-Johnson syndrome), and internal organ involvement
  - May be related to medication or herpes simplex viral infection
  - Erythematous macules, papules, and plaques
    - May have vesicles or bullae
- Erythema nodosum
  - Erythematous plaques and nodules predominantly on shins
  - Septal panniculitis with mixed inflammatory infiltrate
- Drug eruptions
  - Erythematous patches
  - If fixed, may be single patch occurring in same location
  - Resolves with removal of offending medication
  - Eosinophils, dyskeratotic keratinocytes present
- Cellulitis
  - Large single plaque clinically
  - Involves lower extremities most commonly
  - Patients often have fever and often feel lethargic

## SELECTED REFERENCES

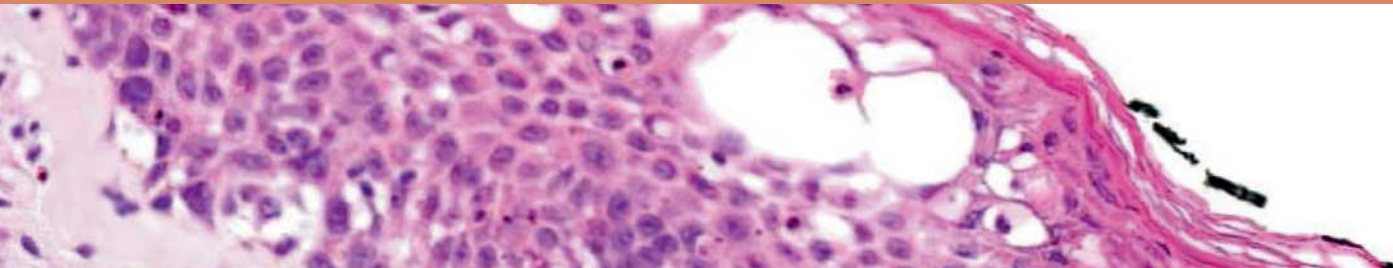
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## SECTION 17

# Nutritional Deficiencies



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# Necrolytic Acral Erythema

## KEY FACTS

### CLINICAL ISSUES

- Treatment of underlying hepatitis C virus (HCV) improves symptoms of necrolytic acral erythema (NAE)
- Associated with chronic hepatitis C infection
- Prevalence of NAE in HCV seropositive populations is low (1.7% in study of 300 HCV-positive individuals)
- Incidence may be decreasing as efficacious treatment for hepatitis C becomes widely available

### MACROSCOPIC

- Erythematous lesions with adherent scale and crust formation
- Erosions, vesicles, and pustule formation may be present
- Symmetrically involves dorsal feet, less frequently lower legs and dorsal hands

### MICROSCOPIC

- Early lesions are subtle and nonspecific
- Progressing lesions

- Confluent parakeratosis
- Decreased or absent granular cell layer
- Epidermal spongiosis with pallor of superficial keratinocytes
- Pigment incontinence
- Papillary dermal lymphocytic infiltrate
- Well-developed lesions
  - Confluent parakeratosis
  - Marked pallor of superficial keratinocytes with cytoplasmic vacuolization and necrosis

### ANCILLARY TESTS

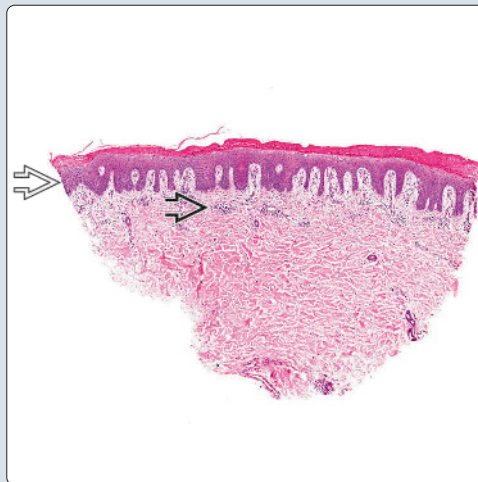
- Serology for hepatitis C along with other hepatitises (hepatitis A, hepatitis B, HIV)

### TOP DIFFERENTIAL DIAGNOSES

- Acrodermatitis enteropathica, necrolytic migratory erythema, pellagra, acrokeratosis paraneoplastica, psoriasis

**Hyperkeratosis, Acanthosis, and Superficial Dermal Infiltrate**

(Left) Low magnification shows hyperkeratosis and acanthosis of the epidermis and a mild inflammatory infiltrate limited to the superficial dermis. (Right) Parakeratosis overlies pallor and early ballooning of superficial keratinocytes. There is also psoriasiform acanthosis of the epidermis and a mild perivascular infiltrate in the superficial dermis.

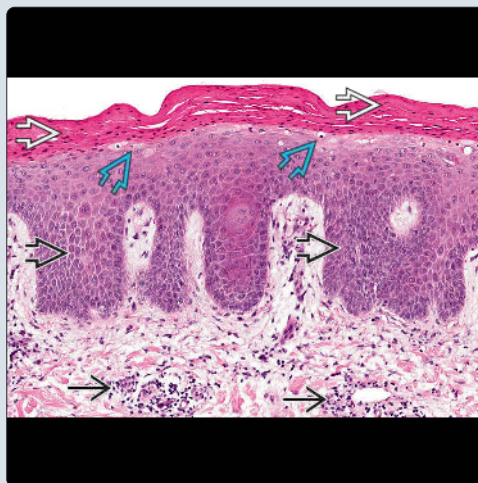


**Parakeratosis, Pallor of Keratinocytes, and Psoriasiform Hyperplasia**



**Confluent Parakeratosis, Keratinocyte Pallor, and Regular Acanthosis**

(Left) Confluent parakeratosis, subtle superficial keratinocyte pallor, epidermal acanthosis, and mild dermal perivascular infiltrate are typical for necrolytic acral erythema. (Right) High magnification demonstrates early ballooning degeneration of superficial keratinocytes with overlying parakeratosis.



**Ballooning of Keratinocytes Beneath Parakeratosis**





## TERMINOLOGY

### Abbreviations

- Necrolytic acral erythema (NAE)

### Definitions

- Psoriasiform cutaneous rash with characteristically acral distribution associated with chronic hepatitis C virus (HCV) infection and zinc deficiency

## ETIOLOGY/PATHOGENESIS

### Associated With Hepatitis C

- Rare hepatitis C seronegative cases of NAE have been found to have zinc deficiency

### Debate Over Whether NAE Is Subtype of Necrolytic Migratory Erythema or Distinct Entity

- Unique clinical presentation of NAE may favor its classification as unique disease entity

## CLINICAL ISSUES

### Epidemiology

- Associated with chronic hepatitis C infection
  - Prevalence of NAE in HCV seropositive populations is low (1.7% in one study)
  - In rare cases of HCV, negative NAE may be related to underlying zinc deficiency

### Presentation

- Acral distribution of dusky, erythematous plaques with adherent scale
- Similar appearance to psoriasis but lacking Auspitz sign of pinpoint bleeding with removal of scale
- Lesions may be intensely pruritic or have painful burning

### Treatment

- Treatment of underlying hepatitis C improves symptoms of NAE
  - Combination therapy with ribavirin and interferon
  - Interferon monotherapy alone can be helpful
- Supplementation with zinc and amino acids also improves clinical manifestations of NAE

### Prognosis

- Often follows relapsing and remitting course that mirrors course of hepatitis C disease
- Morbidity and mortality comes primarily from underlying hepatitis C infection

## MACROSCOPIC

### General Features

- Erythematous lesions with adherent scale and crust formation
- Erosions, vesicles, and pustule formation may be present
- Impetiginization of cutaneous lesions is not uncommon
- Symmetrically involves dorsal feet, less frequently lower legs and dorsal hands

## MICROSCOPIC

### Histologic Features

- Early lesions are subtle and nonspecific
  - Parakeratosis with alternating orthokeratosis
- Progressing lesions
  - Confluent parakeratosis, decreased or absent granular cell layer, epidermal spongiosis with pallor of superficial keratinocytes, pigment incontinence, papillary dermal lymphocytic infiltrate
  - Dyskeratosis not prominent feature
- Well-developed lesions
  - Confluent parakeratosis, marked pallor of superficial keratinocytes with cytoplasmic vacuolization and necrosis
  - Intraepidermal vesicle formation is common and subcorneal pustule formation may be indicative of secondary impetiginization

## ANCILLARY TESTS

### Serologic Testing

- Serology for hepatitis C along with other hepatitides (hepatitis A, hepatitis B, HIV)

### Chemistry Panels and Liver Function Tests

- Evaluate for nutritional deficiencies and hepatic disease

## DIFFERENTIAL DIAGNOSIS

### Acrodermatitis Enteropathica

- Bullous dermatitis with erythema and superficial erosions
- Associated with inherited (presents in infancy) or acquired (presents in adulthood) zinc deficiency
- Characteristic lesions are perioral, perianal/gluteal, and on extremities
- Histology identical to NAE

### Necrolytic Migratory Erythema

- Associated with hyperglucagonemia (typically due to glucagonoma); clinically similar appearance to acrodermatitis enteropathica; histology identical to NAE

### Pellagra

- Niacin (vitamin B3) deficiency; erythematous scaling dermatitis with erosion over sun-exposed skin; histology identical to NAE

### Acrokeratosis Paraneoplastica

- Acral psoriasiform plaques associated with underlying malignancy; histology identical to NAE

### Psoriasis

- Can be clinically similar to NAE; confluent parakeratosis overlying regular epidermal acanthosis, thinning of suprapapillary plates with dilated capillaries in dermal papillae

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## KEY FACTS

### CLINICAL ISSUES

- Dermatitis, diarrhea, and dementia (3 Ds)
- Risk factors include: Dietary deficiency, alcoholism, anorexia nervosa, malabsorption, carcinoid syndrome, Hartnup disease, isoniazid, 6-mercaptopurine, 5-fluoruracil

### MICROSCOPIC

- Nonspecific hyperkeratosis, parakeratosis, acanthosis
- Keratinocyte vacuolation with increased melanin in epidermis
- Telangiectasia and perivascular inflammatory infiltrate in superficial dermis
- May show psoriasiform hyperplasia

### TOP DIFFERENTIAL DIAGNOSES

- Necrolytic migratory erythema
- Acrodermatitis enteropathica
- Porphyria cutanea tarda

### DIAGNOSTIC CHECKLIST

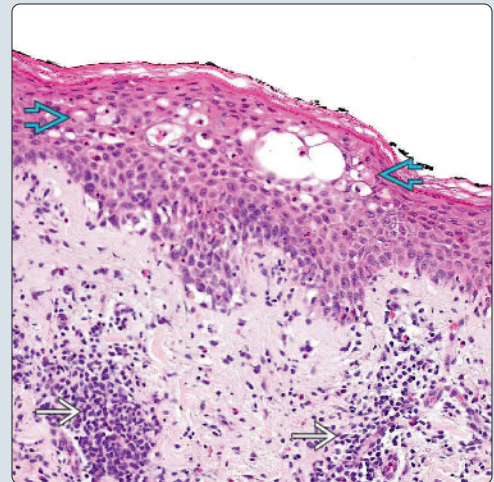
- Clinical features
  - Severe photosensitive rash, desquamation, and vesiculation on sun-exposed areas
  - Cheilosis, glossitis, angular stomatitis, oral or perianal sores
  - Nausea, abdominal pain, gastritis, diarrhea
  - Headache, depression, ataxia, delirium, coma
- Pathologic interpretation pearls
  - Diagnosis is dependent on clinicopathologic correlation
  - Histologically indistinguishable from acrodermatitis enteropathica and similar to necrolytic migratory erythema

**Symmetric Erythematous Blistering on Photo-Exposed Sites**

(Left) Clinical photograph shows symmetric erythematous blistering and scaling erosions over photoexposed areas of the dorsal feet in a patient with pellagra. (Courtesy A. Dominguez, MD.) (Right) Hematoxylin and eosin shows ballooning degeneration of keratinocytes in the mid-to-upper epidermis with a loss of the granular cell layer. A moderate dermal perivascular lymphocytic inflammation is present.

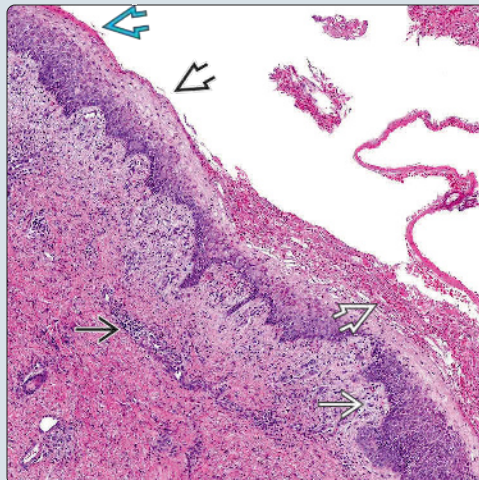


**Ballooning Degeneration and Perivascular Infiltrate**

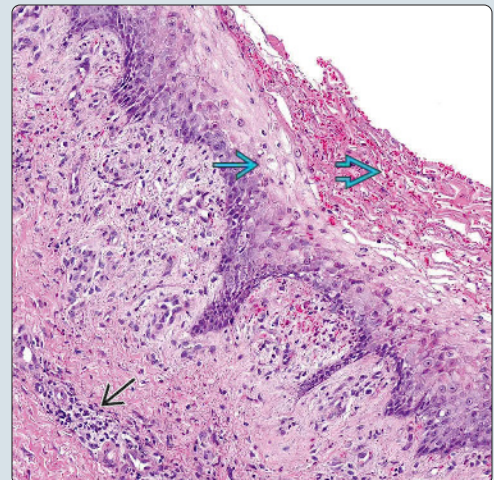


**Epidermal Necrosis, Parakeratosis, and Dermal Infiltrate**

(Left) Parakeratosis, hypogranulosis, superficial keratinocytic necrosis, papillary dermal edema, and superficial perivascular lymphocytic infiltrate are shown. (Right) Early ballooning degeneration of keratinocytes with superficial epidermal necrosis is shown. Dermal telangiectasia and perivascular lymphocytic infiltrate are also present.



**Ballooning Degeneration With Necrosis**





## TERMINOLOGY

### Synonyms

- Vitamin B3 (niacin) deficiency

### Definitions

- Classic triad of dermatitis, diarrhea, and dementia
- Severe photosensitive rash, desquamation, and keratosis on sun-exposed areas
- Other features include cheilosis, glossitis, angular stomatitis, oral or perianal sores

## ETIOLOGY/PATHOGENESIS

### Nutritional Deficiency

- Deficiency of nicotinic acid (niacin, vitamin B3) or tryptophan (precursor) results in decreased NAD and NADP production

### Risk Factors

- Dietary deficiency
- Alcoholism
- Anorexia nervosa
- Malabsorption from gastrointestinal disease
- Carcinoid syndrome (excessive use of tryptophan to form serotonin)
- Hartnup disease
- Multiple myeloma

### Drugs

- Isoniazid
- 6-mercaptopurine
- 5-fluoruracil

## CLINICAL ISSUES

### Epidemiology

- Age
  - Most commonly adults (chronic deficiency); can occur in severely nutritionally deprived children

### Presentation

- Triad: Dermatitis, diarrhea, and dementia (3 Ds)
- Dermatitis
  - Painful, sharply demarcated, symmetric erythematous plaques on photoexposed areas
    - Desquamation
    - Vesicles
    - Keratosis
    - Angular stomatitis
    - Oral and perianal sores

### Prognosis

- Some neurologic complications are irreversible (nerve damage)
- Most symptoms resolve rapidly with treatment
- If untreated, lethal within few years
- Morbidity is associated with end-organ damage, especially neurologic sequelae

## MACROSCOPIC

### General Features

- Often resembles sunburn
  - Red painful plaques with vesicles and desquamation

## MICROSCOPIC

### Histologic Features

- Nonspecific, similar to other nutritional deficiencies
- Hyperkeratosis, parakeratosis, acanthosis
- Psoriasiform hyperplasia may be evident
- Increased melanin and ballooning keratinocytes in upper epidermis
- Telangiectasia and perivascular inflammatory infiltrate

## DIFFERENTIAL DIAGNOSIS

### Necrolytic Migratory Erythema

- Keratinocyte vacuolation, necrosis and intraepidermal vesiculation, suprabasal acantholysis

### Acrodermatitis Enteropathica

- Inherited zinc malabsorption disorder, histologically indistinguishable from pellagra
- Clinically appears in infancy, no improvement with vitamin B supplementation/replacement

### Porphyrria Cutanea Tarda

- Cutaneous bullae formation, elevated urine porphyrins, liver function test abnormalities

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Classic Triad of 3 Ds: dermatitis, diarrhea, dementia
- Severe photosensitive rash and blistering on face, chest, and dorsal aspects of hands, arms, and feet
- Cheilosis, glossitis, angular stomatitis, oral or perianal sores may be present

### Pathologic Interpretation Pearls

- Keratinocyte vacuolation ("ballooning") of upper epidermis
- Increased epidermal melanin
- Telangiectasia and perivascular inflammatory infiltrate in superficial dermis

## SELECTED REFERENCES

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## KEY FACTS

### CLINICAL ISSUES

- Constitutional symptoms: Anorexia, lethargy, weight loss, depression, neuropathy, and pain
- Intraarticular and intramuscular hemorrhage with secondary pain and limited mobility
- Poor wound healing
- Gingival swelling and bleeding
- Treatment includes oral ascorbic acid supplementation; parenteral supplementation may be indicated in cases of malabsorptive disorders

### MACROSCOPIC

- Perifollicular hemorrhage, spontaneous or induced by minimal trauma
- Abnormal hair shafts and fragmented hairs leading to alopecia
- "Woody" edema of lower extremities
- Gingival abnormalities such as gingivitis, gum swelling, and bleeding

### MICROSCOPIC

- Dilated and plugged hair follicles
- Perifollicular inflammation with chronic inflammatory cells and erythrocyte extravasation
- "Corkscrew" and "swan-neck" hair shaft deformities and fragmented hairs

### ANCILLARY TESTS

- Serum levels of ascorbic acid < 2.5 mg/L suggests scurvy

### DIAGNOSTIC CHECKLIST

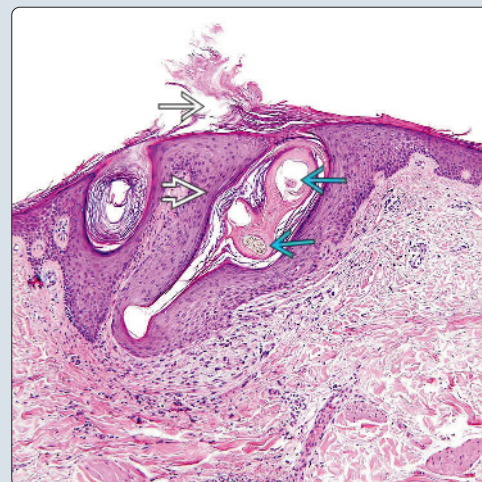
- Scurvy is primarily clinical diagnosis
  - Dietary history lacking in fruits and vegetables or malabsorptive state
- Improvement of symptoms with ascorbic acid supplementation, combined with clinical history consistent with malabsorption or decreased dietary intake is diagnostic of scurvy

**Abnormal-Shaped Hair Shaft With Hyperkeratosis**

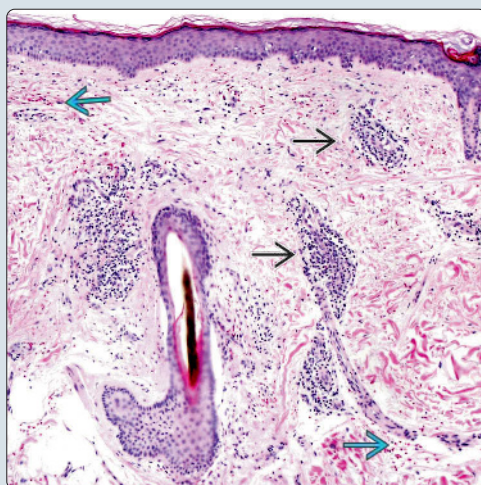


(Left) A biopsy shows the characteristic corkscrew abnormality of hair shafts (visualized as multiple hair shaft cross sections within a single, dilated follicle). There are also perifollicular hyperkeratosis, a dilated follicular ostium, and a perifollicular lymphocytic infiltrate. (Right) Another biopsy of the corkscrew hair abnormality shows multiple hair shaft cross sections within a dilated follicle and associated perifollicular hyperkeratosis.

**Corkscrew-Shaped Hair Shaft and Follicular Hyperkeratosis**

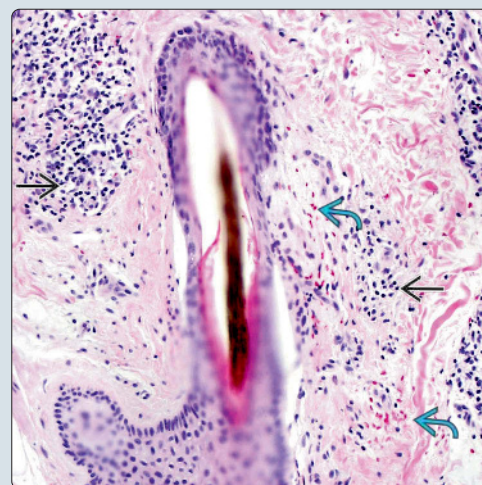


**Chronic Perifollicular Infiltrate With Extravasated Red Blood Cells**



(Left) Another biopsy of scurvy demonstrates a chronic perivascular infiltrate with areas demonstrating extravasated red blood cells. (Right) A higher power view from a biopsy of scurvy demonstrates perifollicular extravasation of red blood cells with an associated chronic inflammatory infiltrate.

**Perifollicular Red Blood Cell Extravasation**





## TERMINOLOGY

### Synonyms

- Barlow disease (infantile scurvy)
  - Not to be confused with Barlow syndrome (mitral valve prolapse)
- Moeller disease, Cheadle disease (infantile scurvy)

### Definitions

- Cutaneous and mucosal disease due to ascorbic acid (vitamin C) deficiency

## ETIOLOGY/PATHOGENESIS

### Function of Ascorbic Acid

- Essential cofactor for prolyl and lysyl hydroxylases necessary for collagen synthesis

### Source of Ascorbic Acid

- Not stored or synthesized in body
- Exogenous intake from foods such as fruits and vegetables is necessary
- Deficiency caused by inadequate intake from diet or impaired gut absorption in ileum

### Deficiency of Ascorbic Acid

- Deficiency results in incomplete hydroxylation of procollagen precursors
- Deficiency manifests clinically in collagen-rich tissues: Skin, gums, vessels

## CLINICAL ISSUES

### Epidemiology

- Uncommon in developed countries
- Risk factors poverty, elderly age, homelessness, chronic alcoholism, psychiatric disorders, poor access to food, restricted diets, and malabsorptive intestinal states (Crohn, large resections, etc.)

### Presentation

- Perifollicular petechiae, purpura, and ecchymoses commonly buttocks and lower extremities
- Intraarticular and intramuscular hemorrhage with secondary pain and limited mobility
- Gingival swelling and bleeding
- Lower extremity "woody" edema
- Poor wound healing
- Alopecia
- Constitutional symptoms: Anorexia, lethargy, weight loss, depression, neuropathy, and pain

### Treatment

- Oral ascorbic acid supplementation
  - 1,000 mg daily, in divided doses for optimal absorption
- Parenteral supplementation may be indicated in cases of malabsorptive disorders

### Prognosis

- Rapid improvement in symptoms with replenishment of ascorbic acid
  - Constitutional symptoms improve within 24 hours
  - Cutaneous manifestations generally resolve within 2-4 weeks

- Long-term supplementation may be necessary if underlying cause of deficiency cannot be corrected

## MACROSCOPIC

### General Features

- Perifollicular hemorrhage, spontaneous or induced by minimal trauma
- Abnormal hair shafts and fragmented hairs leading to alopecia
- "Woody" edema of lower extremities
- Gingival abnormalities such as gingivitis, gum swelling, and bleeding

## MICROSCOPIC

### Histologic Features

- Perifollicular inflammation with chronic inflammatory cells and erythrocyte extravasation
- Perifollicular hyperkeratosis overlying dilated and plugged hair follicles
- "Corkscrew" and "swan-neck" hair shaft deformities and fragmented hairs

## ANCILLARY TESTS

### Serum Ascorbic Acid Level

- Indicates recent intake levels not total body storage
- < 2.5 mg/L suggests scurvy

### Nonspecific Laboratory Findings

- Anemia from increased bleeding
- Concomitant folate and iron deficiencies are common

## DIFFERENTIAL DIAGNOSIS

### Keratosis Pilaris

- Follicular hyperkeratosis, keratin plugging, and mild perifollicular inflammation
- Lacks perifollicular hemorrhage and dysmorphic hair shafts

### Palpable Purpura of Vasculitis or Coagulopathies

- Vasculitis should be evident on biopsy

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Scurvy is primarily clinical diagnosis
  - Dietary history lacking in fruits and vegetables or malabsorptive state
- Improvement of symptoms with ascorbic acid supplementation, combined with clinical history consistent with malabsorption or decreased intake is diagnostic

### Pathologic Interpretation Pearls

- Perifollicular hyperkeratosis, perifollicular hemorrhage with chronic inflammatory infiltrate, and dysmorphic hair shaft forms

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# Acrodermatitis Enteropathica

## KEY FACTS

### TERMINOLOGY

- Rare genetic form of zinc deficiency caused by impaired intestinal absorption of zinc
- Although acquired zinc deficiency can appear identical clinically & histologically, term acrodermatitis enteropathica (AE) is reserved only for genetic form of zinc deficiency

### CLINICAL ISSUES

- Classic triad of periorificial & acral dermatitis, diarrhea, alopecia
  - Skin lesions appear first as
    - Erythematous scaly patches & plaques with erosions & crust, sometimes vesicular/bullous
    - May become psoriasiform over time
  - Typically presents shortly after weaning from breast milk
    - If formula-fed, manifests within first few weeks of life

### MICROSCOPIC

- Histology of AE differs according to stage of lesions

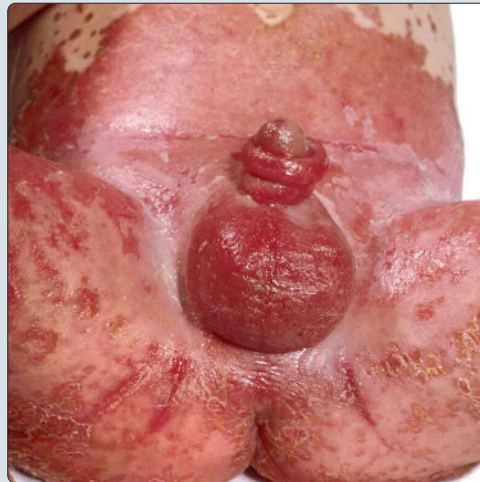
- Early lesions show nonspecific mild parakeratosis alternating with orthokeratosis
- "Necrolysis" of epidermis
  - Cytoplasmic pallor, vacuolization, & ballooning degeneration of keratinocytes in upper layers of epidermis
- May evolve to confluent necrosis of epidermis & intracellular edema resulting in intraepidermal vesiculation
- Chronic lesions may resemble psoriasiform dermatitis with absence of necrolysis or cytoplasmic pallor

### TOP DIFFERENTIAL DIAGNOSES

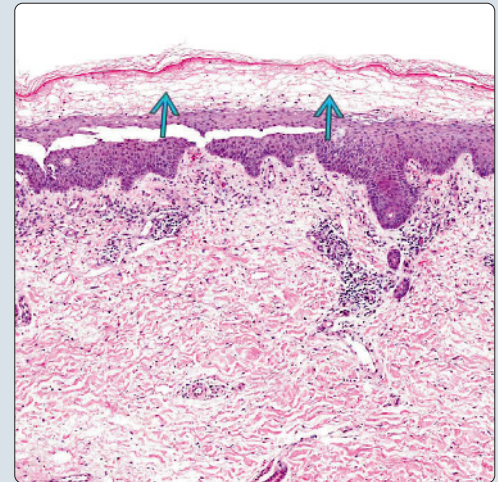
- Considerable histologic overlap/ often indistinguishable with necrolytic migratory erythema, necrolytic acral erythema, pellagra
- Psoriasis
- Bullous lichen planus

#### Erythematous Scaly Plaques

(Left) Erythematous, scaly plaques with extensive erosion are present in this infant. (Courtesy H. Pride, MD.) (Right) There is marked cytoplasmic pallor in the upper epidermis [\[E\]](#).

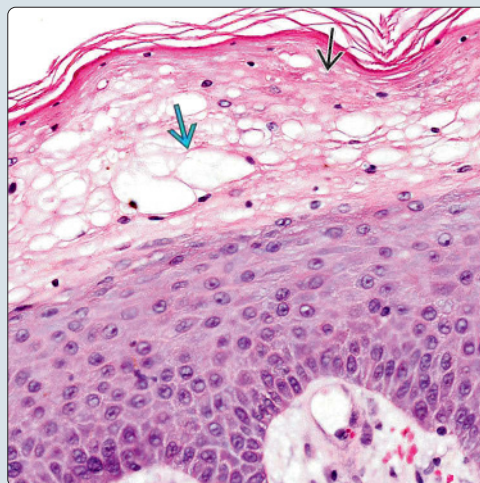


#### Cytoplasmic Pallor in Upper Epidermis



#### Cytoplasmic Pallor & Vacuolization of Cells

(Left) There is marked cytoplasmic pallor [\[E\]](#) & vacuolization [\[E\]](#). Note the diminution of granular layer. (Right) Chronic lesions of acrodermatitis enteropathica show confluent parakeratosis [\[E\]](#) and psoriasiform hyperplasia. However, subtle cytoplasmic pallor of keratinocytes with pyknotic nuclei in the uppermost layers of epidermis is still identifiable [\[E\]](#).



#### Parakeratosis With Cytoplasmic Pallor of Keratinocytes





## TERMINOLOGY

### Abbreviations

- Acrodermatitis enteropathica (AE)

### Definitions

- Rare genetic form of zinc deficiency caused by impaired intestinal absorption of zinc
- Although acquired zinc deficiency can appear identical clinically & histologically, term AE is reserved only for genetic form of zinc deficiency

## ETIOLOGY/PATHOGENESIS

### Genetic

- Autosomal recessive disorder of zinc deficiency due to impaired intestinal absorption of zinc
  - Result of mutation in *SLC39A4* gene encoding zinc transporter protein ZIP4

### Acquired

- Inadequate intake of zinc: Malnourishment, alcoholism, restrictive diets, cystic fibrosis
- Malabsorption of zinc: Cystic fibrosis, inflammatory bowel disease, bariatric surgery
- Chronic diseases: HIV infection, malignancy, chronic renal disease
- Medications that alter zinc metabolism: Thiazides, loop diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, penicillamine

## CLINICAL ISSUES

### Presentation

- Classic triad of periorificial & acral dermatitis, diarrhea, alopecia; however, only 20% present with all 3 signs
  - Erythematous scaly patches & plaques with erosions & crust, sometimes vesicular/bullous
  - Chronic lesions can become lichenified & psoriasiform
  - Favors perioral, periocular, & perineal/anogenital areas as well as scalp, hands, & feet
  - Nails can be affected with pustular paronychia & dystrophy
  - Hair is fine & sparse, & may cease to grow altogether
  - Acquired zinc deficiency may present with milder symptoms/signs due to slower onset/chronicity
    - Rough dry skin, seborrheic dermatitis-like rash of face & perineum, & poor wound healing
- Breast milk contains zinc-binding ligand that increases bioavailability of zinc; thus onset shortly after weaning
  - If formula-fed, manifests within first few weeks of life

### Treatment

- Oral zinc sulfate or zinc gluconate supplementation
  - Lifelong zinc supplementation necessary with periodic checks of serum zinc levels

### Prognosis

- Rapid & dramatic clinical improvement is noted with treatment
  - This rapid response can confirm diagnosis even in setting of normal serum zinc level

- Longstanding zinc deficiency is associated with frequent infections, delayed wound healing, growth retardation, anorexia, anemia, photophobia, hypogonadism, delayed puberty, & altered mental status

## MICROSCOPIC

### Histologic Features

- Zinc is involved in normal keratinization & zinc deficiency results in keratinocytic degeneration
- Histology of AE differs according to stage of lesions
  - Early lesions show nonspecific mild parakeratosis alternating with orthokeratosis
  - More advanced lesions show "necrolysis"
    - Cytoplasmic pallor, vacuolization, & ballooning degeneration of keratinocytes in upper layers of epidermis
    - Diminution of granular layer & scattered dyskeratotic keratinocytes are present
    - Focal spongiosis is common
    - Marked inflammatory infiltrate, such as lichenoid interface dermatitis, can be seen
  - Lesions may evolve to confluent necrosis of epidermis & intracellular edema resulting in intraepidermal vesiculation
  - Neutrophilic crust & secondary infection by *Candida* & *Staphylococci* are frequently noted
  - Chronic lesions may resemble psoriasiform dermatitis with absence of necrolysis or cytoplasmic pallor

## ANCILLARY TESTS

### Serum Blood Tests

- Zinc level is usually low, but up to 30% of patients have normal zinc level (but with low bioavailability of zinc)
  - No clinical correlation between serum zinc level & severity of AE

## DIFFERENTIAL DIAGNOSIS

### Other Nutritional Deficiencies

- Histologic features of AE & acquired zinc deficiency can be indistinguishable from other nutritional deficiencies such as
  - Necrolytic migratory erythema, necrolytic acral erythema, pellagra, essential fatty acid deficiencies, niacin, biotin, & riboflavin deficiencies
  - Appropriate clinical investigation & prompt improvement of symptoms with zinc supplementation confirm diagnosis of AE

### Psoriasis

- Chronic lesions of AE can be predominantly psoriasiform
- Lacks intracellular edema, cytoplasmic pallor, & dyskeratotic keratinocytes of AE

### Bullous Lichen Planus

- Necrolysis & pallor of keratinocytes of AE are minimal or absent

## SELECTED REFERENCES

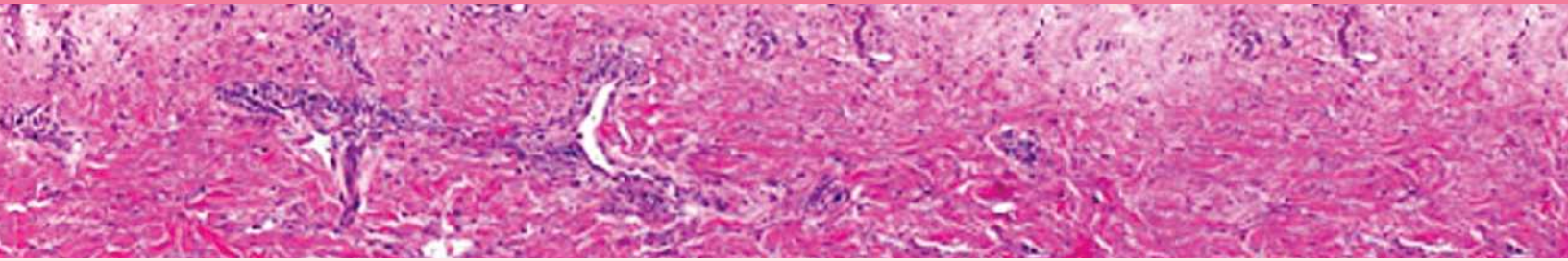
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## SECTION 18

# Photosensitivity Dermatoses



Polymorphous Light Eruption  
Chronic Actinic Dermatitis  
Hydroa Vacciniforme

**508**  
**510**  
**514**

# Polymorphous Light Eruption

## KEY FACTS

### TERMINOLOGY

- Common photosensitivity reaction to UV radiation

### ETIOLOGY/PATHOGENESIS

- Believed to be delayed-type hypersensitivity response (type IV) to photo-induced cutaneous antigens

### CLINICAL ISSUES

- Most common photodermatosis in humans
- Grouped erythematous papules appear on sun-exposed areas in symmetric distribution
- Typically occurs minutes to hours after sun exposure
- Diagnosis typically made by history, clinical findings, and negative rheumatologic work-up
  - Biopsy can be helpful
  - Histopathology can mimic lupus erythematosus, but lupus band test should be negative

### MICROSCOPIC

- Often striking papillary dermal edema

- Lymphocytes in varying numbers typically localized within edematous areas
- Superficial dermal perivascular lymphocytic infiltrate in early lesions
- Often more intense superficial and deep dermal perivascular lymphocytic infiltrate in later lesions

### TOP DIFFERENTIAL DIAGNOSES

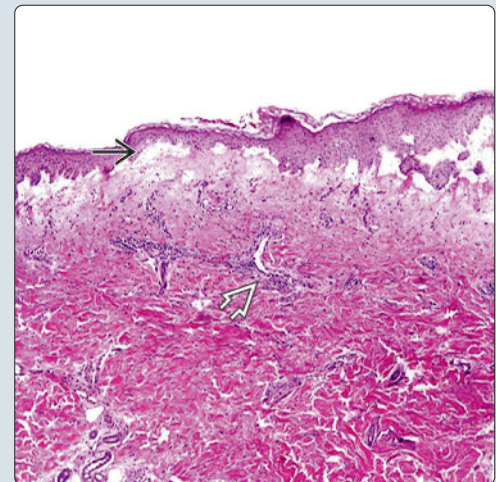
- Lupus
  - Degeneration of basal layer (smudging of basement membrane), epidermal atrophy
- Arthropod bite reaction
  - Eosinophils, less striking papillary edema
- Cellulitis
  - Edema typically filled with neutrophils
- Pernio
  - Superficial and deep perivascular lymphocytic infiltrate with lymphocytes along dermal-epidermal junction (always must exclude lupus erythematosus)

(Left) Polymorphous light eruption often presents clinically as grouped papules on sun-exposed areas, often in a symmetric distribution. This eruption occurred on the backs of the hands in this patient. (Right) PMLE on low power most often demonstrates papillary dermal edema and a superficial perivascular lymphocytic infiltrate.

Grouped Papules on Sun-Exposed Area

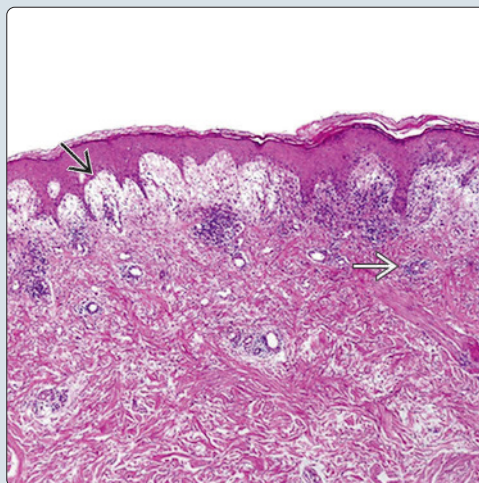


Papillary Dermal Edema

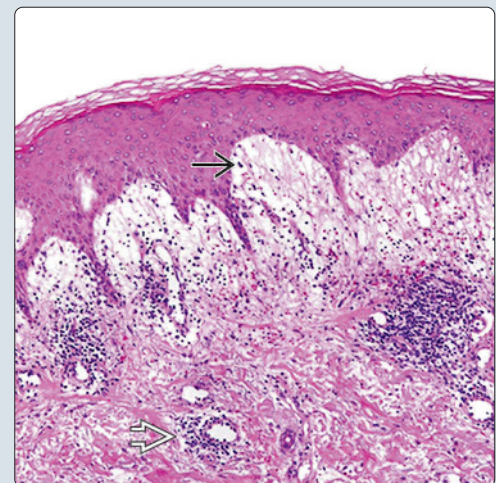


(Left) Marked papillary dermal edema infiltrated with lymphocytes and a tight superficial perivascular lymphocytic infiltrate are the hallmarks of PMLE. (Right) High-power view of PMLE demonstrates lymphocytes infiltrating an edematous papillary dermis and coat sleeve superficial perivascular lymphocytes.

Tight Perivascular Lymphocytic Infiltrate



Lymphocytes Within Papillary Dermal Edema





## TERMINOLOGY

### Abbreviations

- Polymorphous light eruption (PMLE)

### Definitions

- Common photosensitivity reaction to UV radiation

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- Etiology unknown
- Believed to be delayed-type hypersensitivity response (type IV) to photo-induced cutaneous antigens
  - Usually due to UVA
    - Rays through window glass may also be causative

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Most common photodermatosis in humans
  - Varies according to country, but in USA estimated to affect  $\geq 10\%$  of population
- Age
  - Peak incidence in 3rd and 4th decades
- Sex
  - F > M
- Ethnicity
  - Occurs in all races
  - Much more common with Native American ancestry

### Presentation

- Grouped erythematous papules appear on sun-exposed areas in symmetric distribution
  - Typically occurs minutes to hours after sun exposure
- Papules, plaques, and rarely vesicles can occur
- In patients of color, pinpoint papules often occur
- Malaise, fever, headache, and nausea may accompany lesions, but systemic symptoms are not common

### Treatment

- Drugs
  - Topical or oral corticosteroids are best treatment once cutaneous lesions have occurred
- Prophylaxis
  - Desensitization using narrowband UVB therapy 2-3 times/week is probably most effective
  - UVA and UVB sunscreens may be of help
  - Antimalarials, especially hydroxychloroquine, can provide some protection from outbreaks
  - Photoprotective clothing

### Prognosis

- With sun protection from clothes and sunscreens  $\pm$  antimalarials, can usually be controlled

## MICROSCOPIC

### Histologic Features

- Often striking papillary dermal edema
  - Lymphocytes in varying numbers typically localized within edematous areas

- Typically more intense on glabrous skin
- Superficial dermal perivascular coat sleeve-like lymphocytic infiltrate in early lesions
- Often more intense superficial and deep dermal perivascular lymphocytic infiltrate in later lesions
- Epidermis may be normal or show
  - Vacuolization of basal cells, lower epidermal spongiosis, parakeratosis, or acanthosis
- Occasionally histologic findings may be very subtle even in overt clinical disease
  - Diagnosis typically made by history, clinical findings, and negative rheumatologic work-up

## ANCILLARY TESTS

### Direct Immunofluorescence

- Typically shows perivascular IgM and C3 deposition

### Phototesting

- Generally unhelpful but may be positive

## DIFFERENTIAL DIAGNOSIS

### Lupus Erythematosus

- Acute cutaneous lupus erythematosus (LE) and discoid LE can both have marked papillary dermal edema similar to PMLE
- Degeneration of basal layer (smudging of basement membrane), epidermal atrophy
- Dermal mucin deposition (discoid and tumid lesions)
- Clinical history of arthritis, fever, lymphocytopenia, ANA positivity, classic butterfly eruption, or scarring lesions (discoid LE) is helpful
- DIF: IgG and complement positive at dermal-epidermal (DE) junction (positive lupus band test)

### Arthropod Bite Reaction

- Eosinophils (usually absent in PMLE), less striking papillary edema
- Classically wedge shaped (not always seen)
- Clinical history helpful

### Cellulitis

- Can also have striking papillary dermal edema
- Edema typically filled with neutrophils (vs. lymphocytes in PMLE)
- Dermal perivenular lymphocytic infiltrate

### Pernio

- Affects volar skin (vs. nonvolar in PMLE)
- History of hardening with chronic UV exposure (as summer progresses)
- Superficial and deep perivascular lymphocytic infiltrate with lymphocytes along DE junction (always must exclude LE)

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## KEY FACTS

### TERMINOLOGY

- Synonyms include persistent light reaction, photosensitivity dermatitis, and actinic reticuloid

### ETIOLOGY/PATHOGENESIS

- Delayed-type hypersensitivity to ultraviolet A (UVA) or ultraviolet B (UVB) radiation

### CLINICAL ISSUES

- Eruption of erythematous papules and plaques with eczematous features predominantly on sun-exposed areas, including head and neck and distal extremities
- Pruritus and lichenification are common
- Overall, diagnosis of chronic actinic dermatitis requires 3 criteria
  - Persistent photodermatitis of at least 3 months without history of exposure to photosensitizing agent
  - Reduced minimal erythema dose (MED) to UVA, UVB, or visible light

- Compatible histopathology

### MICROSCOPIC

- Spongiotic dermatitis with atypical lymphocytes that mimics mycosis fungoides

### ANCILLARY TESTS

- CD4:CD8 ratio is usually  $\leq 1:1$ , and T-cell receptor (*TCR*) gene rearrangement is negative
- Phototesting demonstrates decreased MEDs to UVA, UVB, or visible light

### TOP DIFFERENTIAL DIAGNOSES

- Cutaneous T-cell lymphoma
- Drug-induced photosensitivity
- Atopic dermatitis
- Airborne contact dermatitis

Lichenified Eczematous Plaques on Sun-Exposed Skin



Chronic actinic dermatitis (CAD) shows lichenified, eczematous plaques on the forearms and dorsal hands. Note the sharp contrast with the non-sun-exposed skin of the thighs.



**TERMINOLOGY****Abbreviations**

- Chronic actinic dermatitis (CAD)

**Synonyms**

- Persistent light reaction
- Photosensitivity dermatitis
- Actinic reticuloid

**Definitions**

- Persistent eczematous photosensitivity of at least 3 months' duration with abnormal phototesting results and histologic findings of spongiosis and atypical lymphocytes

**ETIOLOGY/PATHOGENESIS****Environmental Exposure**

- Enhanced cutaneous immune function, due to preexisting atopy, may result in recognition of endogenous photo-induced allergen with resulting delayed-type hypersensitivity to ultraviolet A (UVA) or ultraviolet B (UVB) radiation over time
- Another theory is that chronically eczematous or photoaged skin may allow easier penetration of airborne antigens but slower antigen removal, leading to immune response

**CLINICAL ISSUES****Epidemiology**

- Age
  - Usually elderly males
- Ethnicity
  - Any race can be affected

**Presentation**

- Eruption of erythematous papules and plaques with eczematous features predominantly on sun-exposed areas, including head and neck and distal extremities
- However, extension to sun-protected areas is frequent, and patients may present with erythroderma
- Pruritus and lichenification are common
- Contact dermatitis or sensitivity to hexachlorophene; sunscreen ingredients, such as oxybenzone, musk ambrette; *Compositae* plant extracts, such as sesquiterpene lactone, para-phenylenediamine, carba mix, and pesticides, confirmed by patch or photopatch testing, are present in over 70% of patients
- Atopic dermatitis and HIV infection are also associated with CAD
- Overall, diagnosis of CAD requires 3 criteria
  - Persistent photodermatitis of at least 3 months without history of exposure to photosensitizing agent
  - Reduced minimal erythema dose (MED) to UVA, UVB, or visible light
  - Compatible histopathology

**Treatment**

- Surgical approaches
  - Dermabrasion has been used to successfully treat case of CAD refractory to medical therapy
- Drugs

- In addition to sun avoidance, initial management includes use of sunscreens, topical corticosteroids, or topical tacrolimus or pimecrolimus
- However, more aggressive treatments are often required, such as psoralen with UVA (PUVA) or antimalarials
- Systemic immunosuppressive agents with reported efficacy include prednisone, methotrexate, azathioprine, cyclosporine, and mycophenolate mofetil
  - Based on data from randomized controlled trial and retrospective studies, azathioprine has been most effective of these agents
- Sunlight avoidance
  - Initial management requires sunlight avoidance

**Prognosis**

- CAD is frequently refractory, and treatment can be difficult
- In study of natural history of CAD, improvement or resolution occurs in up to 90% of patients within 15 years

**MICROSCOPIC****Histologic Features**

- Tissue reaction pattern is spongiotic
- Universal features include acanthosis, spongiosis, superficial and deep lymphocytic infiltrate, papillary dermal fibroplasia, melanophages, and stellate or multinucleated dendritic cells
  - Collections of these dendritic cells may give appearance of focal granulomatous inflammation
- Plasma cells, eosinophils, medium to large reactive lymphocytes with nuclear atypia, solar elastosis, and epidermal and follicular exocytosis are commonly present
- Surface changes, such as parakeratosis and serum crust, may be identified
- Pautrier-like microabscesses (lymphocytes with spongiosis) are occasionally seen

**ANCILLARY TESTS****Immunohistochemistry**

- Majority of the CD3(+) intraepidermal lymphocytes in CAD are CD8(+) (T suppressor-cytotoxic) cells, in contrast to findings in cutaneous T-cell lymphoma
  - There is also slight predominance of CD8(+) lymphocytes in dermal infiltrate, and 80% of cases demonstrate CD4:CD8 ratio  $\leq$  1:1
  - Majority of CD3(+) lymphocytes are also positive for  $\beta$ -chain constant region of T-cell receptor (BF1)
- Mononuclear dendritic cells are reactive for factor XIIIa, while multinucleated cells are not

**Phototesting**

- Important component of diagnosis given that all patients with CAD demonstrate decreased MEDs to UVA, UVB, or visible light
- Most patients show decreased MED to both UVA and UVB

**Clonality Studies**

- *TCR* gene rearrangement is negative

**DIFFERENTIAL DIAGNOSIS****Cutaneous T-Cell Lymphoma**

- Based on histopathology alone, CAD is difficult to distinguish from cutaneous T-cell lymphoma (CTCL)
  - Although significant spongiosis is always present in CAD, and presence of stellate or multinucleate dendritic cells in CAD is helpful feature
  - Additionally, photosensitivity (by MED) is absent in CTCL
- CD4(+) (T-helper) cells are predominant in epidermis and dermis of CTCL, in contrast to CD8 predominance seen in CAD
  - Concordance between BF1 and CD3 expression seen in CAD is not present in CTCL
  - Although results of T-cell clonality are variable in CTCL, they are negative in CAD
  - Combination of clinical and immunohistologic findings is usually required to distinguish these 2 diseases

**Drug-Induced Photosensitivity**

- Most photosensitizers absorb UVA within skin, which can be demonstrated with photopatch testing
  - However, without photosensitizer, MEDs are normal
- Distribution of eruption may be similar to that of CAD
- Histopathology is variable and may be lichenoid (photodistributed lichenoid drug eruption), spongiotic (photoallergic eruption), or demonstrate necrotic cells in upper layers of epidermis with sparse inflammation (phototoxic drug eruption)

**Atopic Dermatitis**

- Photosensitivity is common in atopic eczema, and spongiosis is common to both disorders
- However, deep inflammation, lymphocytic atypia, and Pautrier-like microabscesses are not seen in atopic dermatitis

**Airborne Contact Dermatitis**

- Airborne contact dermatitis (ABCD) is reported to occur in majority of patients with CAD and may precede photosensitivity
- Additionally, clinical findings are very similar
  - However, true photosensitivity, established by reduced MEDs on phototesting, are not seen in ABCD
  - ABCD, unlike CAD, improves with avoidance of allergen
- Spongiotic dermatitis is common to both, but lymphocyte atypia is not common feature in ABCD

**DIAGNOSTIC CHECKLIST****Clinically Relevant Pathologic Features**

- Spongiosis and papillary dermal fibroplasia
- Superficial and deep lymphocytic infiltrate
- Atypical lymphocytes
- May have Pautrier-like microabscesses, plasma cells, and eosinophils

**Pathologic Interpretation Pearls**

- Stellate or multinucleated dendritic cells are unique

**SELECTED REFERENCES**

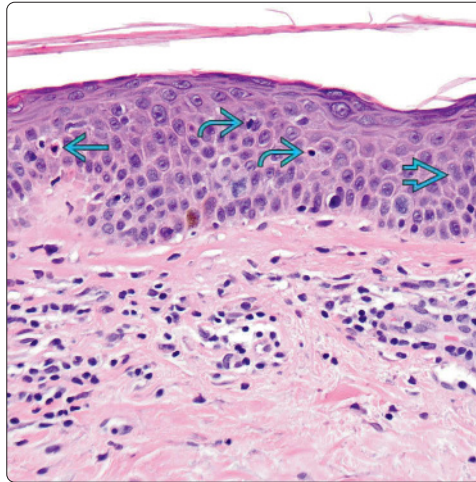
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**Eczematous Plaques With Pruritus**

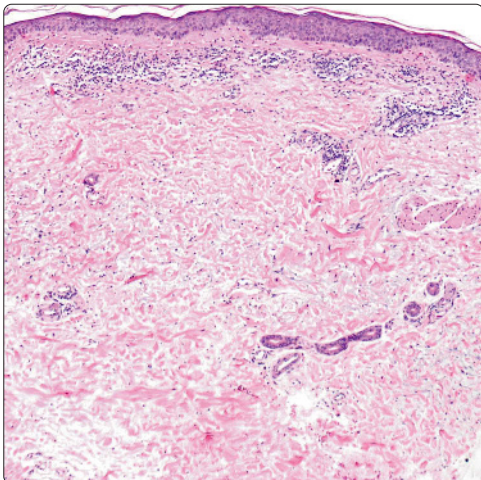


**Spongiosis With Necrotic Keratinocytes**

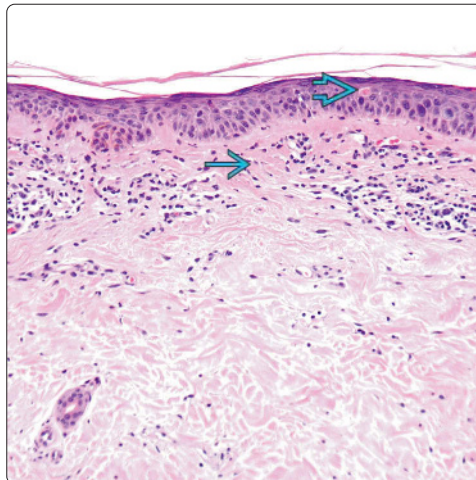


(Left) CAD presents as eczematous plaques on sun-exposed skin of this elderly man. Pruritus was marked. (Right) Histopathology demonstrates subacute spongiosis [blue box] with rare necrotic keratinocytes [blue box] and lymphocytic exocytosis [blue box]. Papillary dermal fibroplasia, indicative of chronicity, is also present. The process is occurring on a background of sun-damaged skin.

**Superficial and Middermal Perivascular Infiltrate**

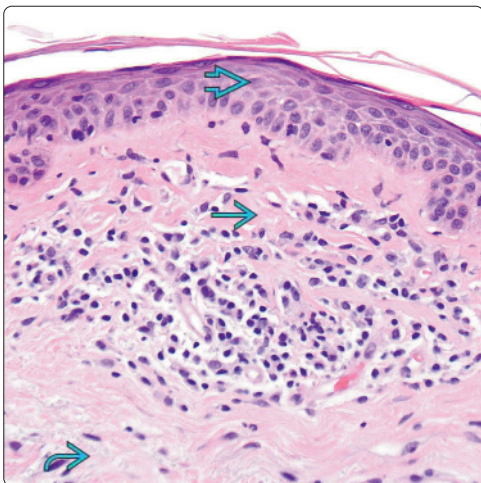


**Subacute Spongiotic Dermatitis**

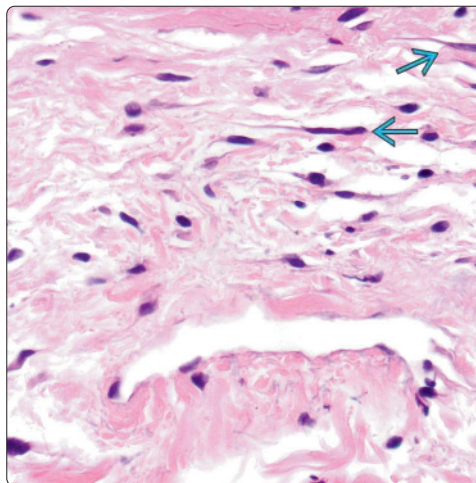


(Left) A low-power view of CAD demonstrates a subacute spongiotic dermatitis with a superficial and middermal perivascular dermatitis. (Right) CAD shows a subacute spongiotic dermatitis with rare necrotic keratinocytes [blue box] in the upper epidermis. Papillary dermal fibroplasia [blue box] is also evident.

**Papillary Dermal Fibroplasia and Solar Elastosis**



**Prominent Dermal Dendrocytes**



(Left) A high-power view of CAD demonstrates subacute spongiosis [blue box], papillary dermal fibroplasia [blue box], and a lymphohistiocytic perivascular dermatitis. Also note solar elastosis [blue box]. (Right) Prominent dermal dendrocytes [blue box], with elongated cytoplasmic processes, in the papillary dermis in a case of CAD are shown.



# Hydroa Vacciniforme

## KEY FACTS

### TERMINOLOGY

- Definition
  - Uncommon recurrent vesicular eruption typically in childhood that occurs in successive outbreaks on sun-exposed sites typically in summer months and heals with varioliform or vacciniiform scars

### CLINICAL ISSUES

- Principally occurs in childhood
- Typically resolves spontaneously by adolescence or early adulthood
- Uniform vesicles and crusts develop several hours or 1-2 days after sun exposure
- Lesions then heal with varioliform scarring

### MICROSCOPIC

- Early lesions show
  - Perivascular lymphohistiocytic infiltrate followed by neutrophils

- Later lesions show
  - Epidermal spongiosis leading to reticular alteration, intraepidermal vesiculation, and confluent epidermal necrosis
  - Vesicles are filled with fibrin and neutrophils

### ANCILLARY TESTS

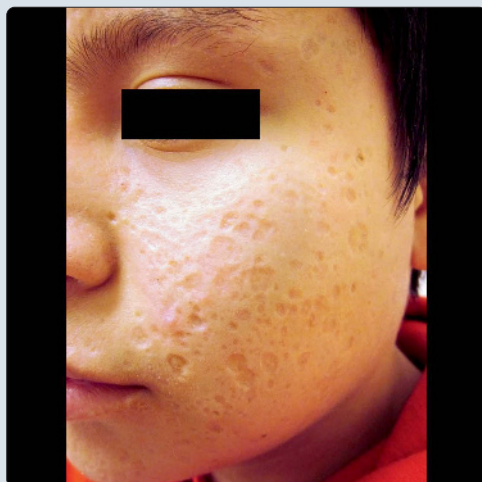
- Should all be within normal limits
- Porphyrin levels should be normal

### TOP DIFFERENTIAL DIAGNOSES

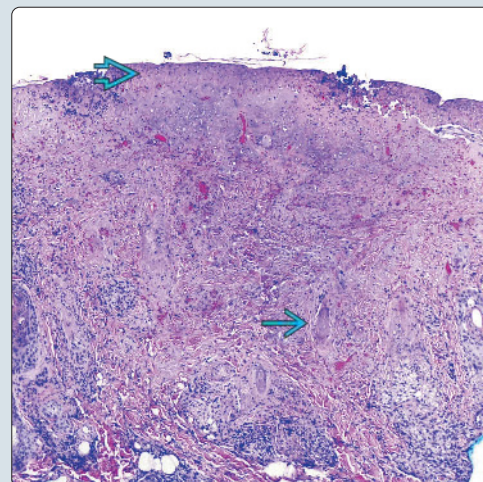
- Histopathologic
  - Polymorphous light eruption
  - Photoallergic dermatitis
  - Phototoxic eruption
  - Actinic prurigo
  - Actinic reticuloid (chronic actinic dermatitis)

### Varioliform Scars With Deep Pox Marks

(Left) Varioliform scars with deep pox marks of irregular sizes and shapes on the cheeks of a child are shown. In hydroa vacciniiforme, these scars are preceded by vesicles that rapidly become deep crusted craters. (Right) A late lesion of hydroa vacciniiforme demonstrates confluent epidermal necrosis [X], hemorrhage, and areas of dermal necrosis [X]. (Courtesy A. Diwan, MD.)

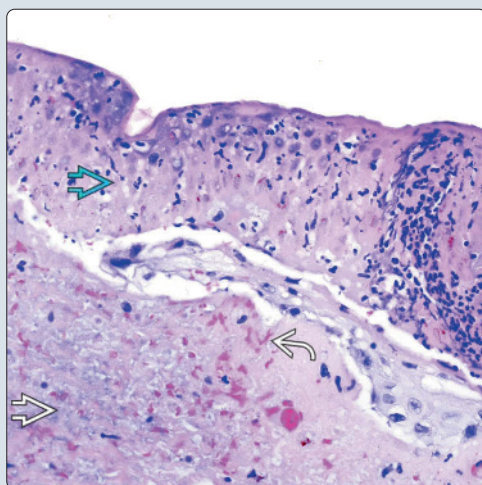


### Epidermal and Dermal Necrosis

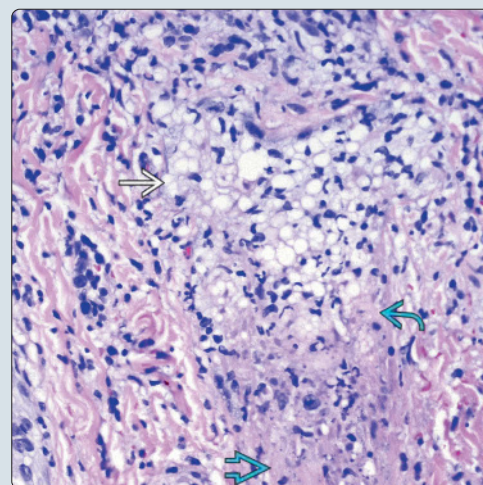


### Confluent Epidermal Necrosis and Hemorrhage

(Left) Higher power view of a late lesion of hydroa vacciniiforme demonstrates confluent epidermal [X] and dermal [X] necrosis as well as areas of hemorrhage [X]. (Courtesy A. Diwan, MD.) (Right) This biopsy demonstrates some areas of spongiosis [X] leading to reticular degeneration [X] and then areas of necrosis [X] with a surrounding chronic inflammatory infiltrate. (Courtesy A. Diwan, MD.)



### Reticular Alteration, Necrosis and Chronic Inflammation





## TERMINOLOGY

### Abbreviations

- Hydroa vacciniforme (HV)

### Synonyms

- Bazin HV
- HV of Bazin
- Summer eruption

### Definitions

- Uncommon recurrent vesicular eruption typically in childhood that occurs in successive outbreaks on sun-exposed sites typically in summer months and heals with varioliform or vacciniiform scars

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Extremely rare
- Age
  - Principally occurs in childhood
  - Typically resolves spontaneously by adolescence or early adulthood
- Sex
  - Males slightly more affected than females

### Presentation

- Uniform vesicles and crusts develop several hours or 1-2 days after sun exposure
  - Lesions then heal with varioliform or vacciniiform scarring
    - Vacciniiforme (from vacciniiform) = resembling vaccinia or cowpox
    - Varioliform = resembling smallpox

### Treatment

- Sun avoidance, appropriate clothing and high SPF sunscreens to prevent recurrences is best treatment
- Adjuvant phototherapy may be considered for photoprotection

### Prognosis

- Most cases resolve spontaneously by adolescence
- Scarring, however, is permanent

## MICROSCOPIC

### Histologic Features

- Early lesions show
  - Epidermal vesicles may occur ± reticular degeneration
  - Dense perivascular lymphohistiocytic infiltrate followed by neutrophils
  - Thrombosis and hemorrhage may occur
- Later lesions show
  - Epidermal spongiosis leading to reticular alteration, intraepidermal vesiculation and confluent epidermal necrosis
    - Vesicles are filled with fibrin and neutrophils
  - Dermal necrosis may also be present with surrounding chronic inflammatory infiltrate

## ANCILLARY TESTS

### Laboratory Tests

- Should all be within normal limits
- Porphyrin levels should be normal

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Polymorphous light eruption
  - No areas of epidermal or dermal necrosis
  - Papillary dermal edema is present, but typically no epidermal changes present
- Photoallergic dermatitis
  - No areas of epidermal or dermal necrosis
  - Typically eosinophils in inflammatory infiltrate
  - Spongiosis without reticular degeneration
- Phototoxic eruption
  - Can demonstrate dyskeratotic keratinocytes, but reticular degeneration usually not seen
  - Dermal areas of necrosis are not seen
- Actinic prurigo
  - Clinically looks like prurigo nodularis but limited to sun-exposed sites
    - Lichenified nodule that is typically hyperkeratotic
    - Sometimes can be large nodules (> 1 cm)
  - Doesn't blister clinically
  - Extremely pruritic clinically
- Actinic reticuloid (chronic actinic dermatitis)
  - Erythematous and indurated clinically
    - Looks like infiltrative disease and is more confluent clinically
  - No blisters clinically

### Clinical

- Erythropoietic protoporphyria
  - More redness (like sunburn), typically not as vesicular as HV
  - Elevated free protoporphyrins
- Polymorphous light eruption (vesicular form)
  - Very rare
  - Typically doesn't blister
- Bullous lupus erythematosus
  - More apt to have background of atrophy, follicular plugging, scarring, and areas of hypo- or hyperpigmentation
    - Blister typically occurs on this background
- Solar urticaria
  - Should be evanescent
  - Typically does not blister
  - Does not scar

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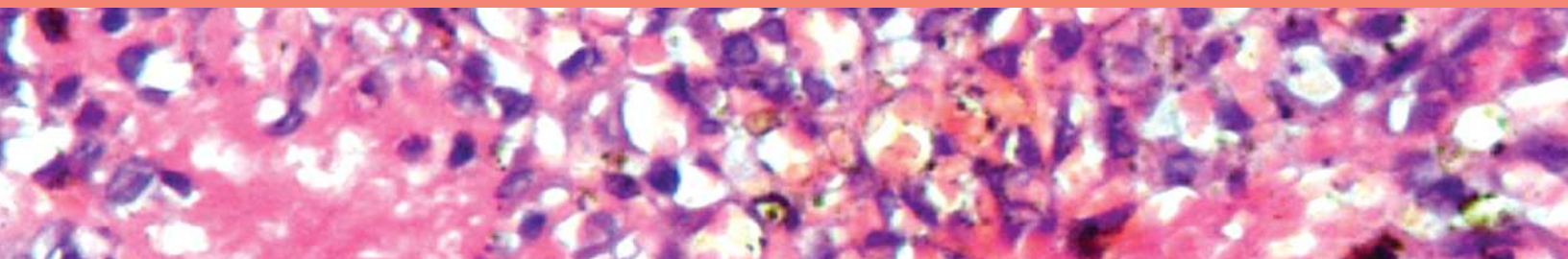
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## SECTION 19

# Bacterial Infections



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## KEY FACTS

### TERMINOLOGY

- Definition
  - Acute, contagious superficial pyogenic infection of skin caused by staphylococci, streptococci, or both

### CLINICAL ISSUES

- Epidemiology
  - Peak incidence during summer and fall
  - Children affected most commonly
  - Face and extremities usually involved
- Nonbullous impetigo
  - Thin-walled vesicles on erythematous base that rupture rapidly, forming honey-colored crusts
- Bullous impetigo
  - Flaccid blisters and tender shallow erosions
- Typically resolves with topical and oral antibiotics

### MICROSCOPIC

- Nonbullous impetigo

- Subcorneal pustule with few acantholytic cells
- Gram-positive cocci sometimes found in pustule or scale crust
- Moderate superficial perivascular and interstitial mixed-cell infiltrate
- Bullous impetigo
  - Subcorneal blister with few neutrophils and some acantholytic cells
  - Rare or absent cocci
  - Sparse superficial perivascular inflammatory infiltrate

### ANCILLARY TESTS

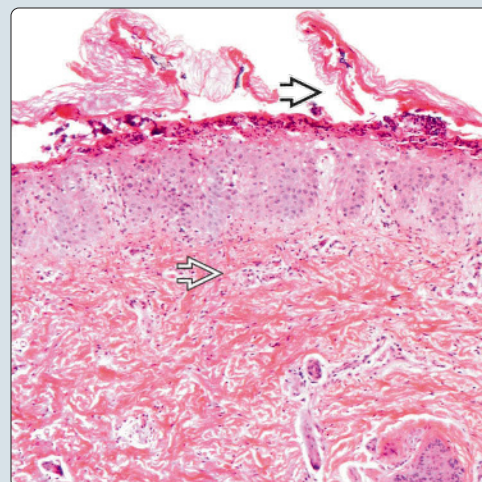
- Gram stain reveals gram-positive cocci

Honey-Colored Crusts in Axilla

(Left) A case of impetigo demonstrates pustules, flaccid bullae, and erosions covered by honey-colored crusts in a circinate configuration. (Right) This H&E section shows a subcorneal pustule with neutrophils and sparse inflammatory cell infiltrate in the dermis in a case of bullous impetigo.



Subcorneal Pustule

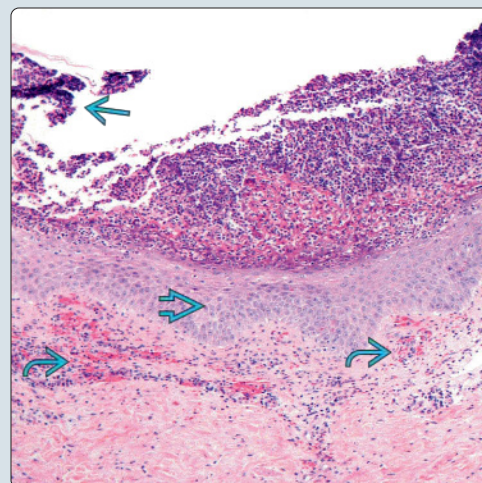


Impetigo of Beard

(Left) Folliculitis of the beard with secondary impetigo is demonstrated by the honey yellow-colored crusting. (Right) Intense neutrophilic subcorneal inflammatory collection with underlying spongiosis and perivascular mixed inflammatory infiltrate is shown.



Intense Neutrophilic Subcorneal Pustule





## TERMINOLOGY

### Synonyms

- Pyoderma
- Nonbullous impetigo
- Impetigo contagiosa of Tilbury-Fox

### Definitions

- Acute, contagious, superficial pyogenic infection of skin caused by staphylococci, streptococci, or both

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- *Staphylococcus aureus*
  - Gram-positive, nonmotile, nonspore-forming, catalase-positive cocci
  - Produce extracellular exfoliative exotoxins (exfoliatin A and B)
- *Streptococcus pyogenes*
  - a.k.a. group A  $\beta$ -hemolytic streptococci
  - Gram-positive, nonmotile, chain-forming, nonspore-forming, oxidase- and catalase-negative cocci

### Pathogenesis

- **Staphylococcal pyodermas**
  - Occur in individuals who are carriers of organism in axillary, inguinal, and perianal areas and anterior nares
  - Predisposing conditions include atopic dermatitis, diabetes mellitus, dialysis, intravenous drug use, and HIV infection
  - Insect bites, dermatophytoses, herpetic infections, varicella, abrasions, lacerations, and thermal burns also contribute to pathogenesis
- **Group A streptococcal pyodermas**
  - Occur following colonization of skin from skin of another individual or from patient's nasopharynx
- **Nonbullous impetigo**
  - Currently *S. aureus* is prominent pathogen responsible for nonbullous impetigo
    - Accounts for 50-60% of cases
    - In past, *S. aureus* and *S. pyogenes* occurred with equal frequency
  - 20-45% of cases are due to combination of *S. aureus* and *S. pyogenes*
  - *S. pyogenes* is still most common cause in developing countries
- **Bullous impetigo**
  - Causative agent is gram-positive, coagulase-positive, group II *S. aureus*, most often phage type 71
  - *S. aureus* exotoxins cause loss of cell adhesion in superficial dermis, producing blisters in granular cell layer of epidermis
  - One of target proteins for exotoxin A is desmoglein-1

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Most common bacterial skin infection and 3rd most common skin disease among children
  - Peak incidence occurs during summer and fall

- Age
  - Both bullous and nonbullous impetigo affect all ages but mostly affect children younger than 6 years of age
  - Bullous impetigo is most common in neonates and infants
- Sex
  - M = F
- Ethnicity
  - Can affect people of all races

### Site

- Any part of body can be involved
- Face and extremities are affected most commonly

### Presentation

- Nonbullous impetigo
  - Initial lesion is thin-walled vesicle on erythematous base
  - Vesicle ruptures rapidly and forms honey-colored crust
  - Individual lesions may extend peripherally with central clearing, resulting in annular or circinate morphologies
  - Satellite lesions in either adjacent areas or other parts of body may appear
  - Regional adenitis with fever and other constitutional symptoms may appear in severe cases
- Bullous impetigo
  - Vesicles rupture less rapidly, become much larger, forming flaccid blisters that persist for few days
  - Blisters leave tender shallow erosions
  - Fever, diarrhea, weakness may occur

### Laboratory Tests

- Diagnosis usually based on history and clinical appearance
- Confirmation of causative organism by culture
- Sensitivity tests for methicillin-resistant staphylococci sometimes necessary
- Urinalysis to evaluate for acute poststreptococcal glomerulonephritis

### Treatment

- Options, risks, complications
  - Usually resolves with topical and oral antibiotics
  - Complications
    - Cellulitis, lymphangitis, ecthyma, erysipelas, arthritis, osteomyelitis
    - Bacteremia, bacterial endocarditis, and septicemia
    - Acute glomerulonephritis in 2-5% of patients with nonbullous impetigo
    - Toxic shock syndrome, staphylococcal scalded skin syndrome, and scarlet fever
- Adjuvant therapy
  - Good personal hygiene
  - Treatment of *S. aureus* nasal carriers and asymptomatic family members
- Drugs
  - Topical antibiotics are used in patients with small or few lesions
    - Mupirocin ointment, retapamulin 1% ointment, fusidic acid 2% ointment, gentamicin, clindamycin
  - Oral antibiotics remain appropriate for many patients
    - Cephalosporins, semisynthetic penicillin, or  $\beta$ -lactam/ $\beta$ -lactamase inhibitor

- Tetracycline, trimethoprim/sulfamethoxazole, clindamycin, or linezolid

## Prognosis

- Some lesions may resolve spontaneously
- Resolution occurs after 7-10 days of antibiotic treatment
  - If not, bacterial culture and sensitivity tests should be performed for methicillin-resistant organisms

## MICROSCOPIC

### Histologic Features

- Nonbullous impetigo
  - Subcorneal pustule with few acantholytic cells
  - Spongiform pustule sometimes present in stratum spinosum beneath subcorneal pustule
  - Thick scale crust with neutrophils
  - Superficial perivascular and interstitial infiltrate with lymphocytes and neutrophils
  - Gram-positive cocci sometimes found in pustule or scale crust
- Bullous impetigo
  - Subcorneal blister that contains few neutrophils and some acantholytic cells
  - Sparse superficial perivascular and interstitial inflammatory infiltrate
  - Rare or absent cocci

## ANCILLARY TESTS

### Gram Stain

- Reveals gram-positive cocci

## DIFFERENTIAL DIAGNOSIS

### Pustular Psoriasis

- Inflammatory disease of genetic nature with localized (palmoplantar) or generalized eruption of sterile pustules
- Subcorneal and spongiform pustules, psoriasiform hyperplasia (can be mild in early lesions), dilated and tortuous capillaries in edematous dermal papillae, mixed inflammatory cell infiltrate with lymphocytes and neutrophils
- No bacteria in neutrophils

### Subcorneal Pustular Dermatitis (Sneddon-Wilkinson Disease)

- Rare, benign, chronic relapsing sterile pustular eruption typically involving flexural sites of trunk and proximal extremities
- Some cases represent variant of pustular psoriasis
- Subcorneal pustule that appears to sit on skin surface with neutrophils, occasional eosinophils, and scattered acantholytic cells
- No bacteria identified on H&E or Gram stains; negative bacterial cultures

### Pustular Fungal Infections (Dermatophytosis and Candidiasis)

- Circular, sharply marginated lesions with vesicles and pustules in dermatophytosis
- Vesicles, pustules, and crusted erosions on skin folds in candidiasis

- Subcorneal pustules, spongiform pustules, variable acanthosis, spongiosis, papillary edema, and perivascular mixed inflammatory cell infiltrate with lymphocytes, neutrophils, and eosinophils
- Spores, hyphae, or pseudohyphae seen on H&E or PAS stains

### Superficial Pemphigus (Pemphigus Foliaceus and Pemphigus Erythematosus)

- Crusted erythematous plaques and shallow erosions with small vesicles along borders involving seborrheic areas
- Subcorneal blister that houses acantholytic cells, fibrin, and some neutrophils
- Sparse to moderate perivascular and interstitial mixed inflammatory cell infiltrate
- Intercellular staining for IgG and C3 throughout epidermis

### Staphylococcal Scalded Skin Syndrome

- Exfoliative dermatitis usually affecting neonates and young children produced by exfoliative toxins secreted by phage group II staphylococci
- Scarlatiniform eruption with extensive blistering and widespread denuded areas
- Subcorneal blister with only rare inflammatory cells and some acantholytic cells
- Minimal or absent dermal inflammation
- No bacteria present

### Pustular Drug Eruptions/Acute Generalized Exanthematous Pustulosis

- Occurrence after ingestion of various drugs, including diltiazem, isoniazid, amoxicillin, cephalosporins
- Sudden appearance of numerous pustules on erythematous background, fever and leukocytosis
- Subcorneal &/or intraepidermal pustules with few acantholytic keratinocytes, and spongiosis
- Superficial perivascular infiltrate of lymphocytes and histiocytes with conspicuous neutrophils and eosinophils

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Superficial infection with *S. aureus* &/or *S. pyogenes*
- Most common in children, especially around mouth, nose, axilla, or groin
- 2 classical forms (nonbullous and bullous) exist

### Pathologic Interpretation Pearls

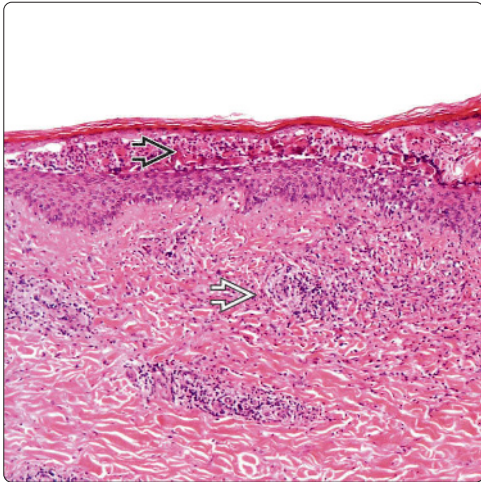
- Subcorneal blister with variable amounts of neutrophils and acantholytic cells
- Gram-positive cocci may be found in blister
- Bullous impetigo, staphylococcal scalded skin syndrome, and superficial pemphigus are indistinguishable histopathologically

## SELECTED REFERENCES

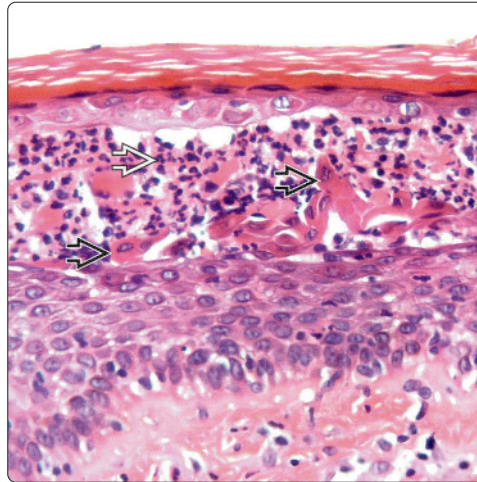
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**Pustular Dermatitis**

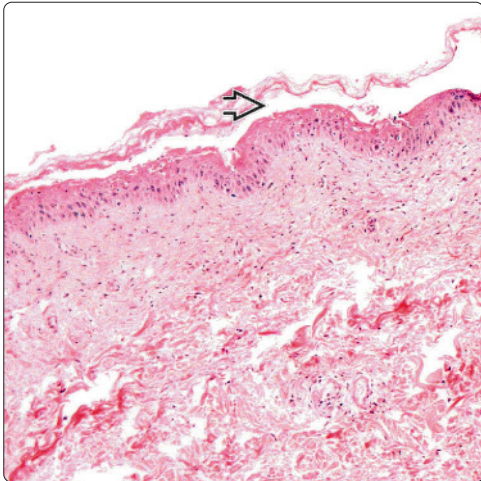


**Acantholytic Cells**

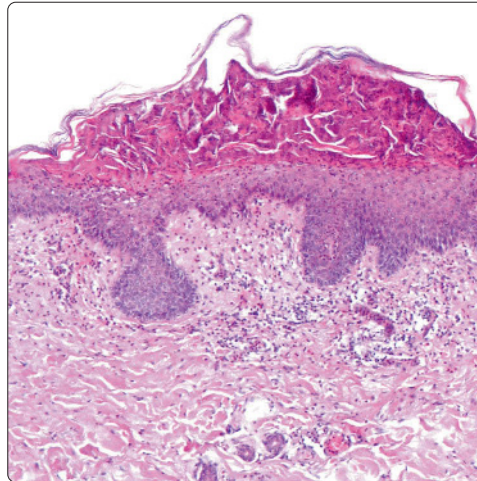


(Left) This case of impetigo contagiosa shows a subcorneal pustular dermatitis with abundant inflammatory cell infiltrate. (Right) Acantholytic cells in a collection of neutrophils can be seen in impetigo. Similar findings can be observed in superficial pemphigus.

**Staphylococcal Scalded Skin Syndrome**

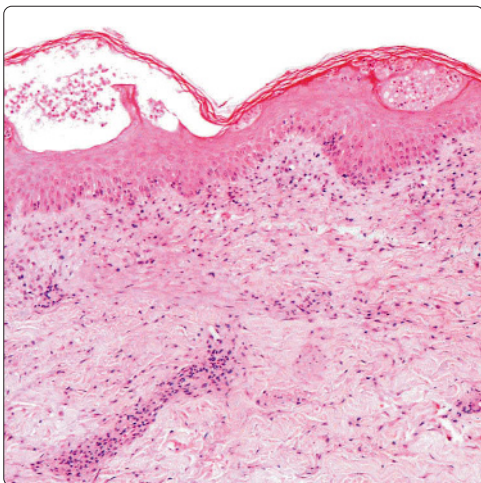


**Subcorneal Blister**

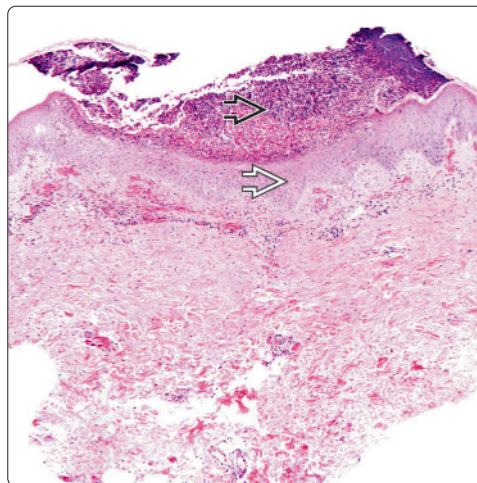


(Left) Staphylococcal scalded skin syndrome is characterized by a cell poor subcorneal blister with minimal dermal inflammation. Bullous impetigo can present with similar changes. (Right) Subcorneal blister with squamous cells, necrotic acantholytic cells, and neutrophils can be seen in both superficial pemphigus (as in this case) and impetigo.

**Pustular Drug Eruption**



**Sneddon-Wilkinson Disease**



(Left) Subcorneal pustules can also be encountered in pustular drug eruption, another mimicker of impetigo. Dermal eosinophils are typically present. (Right) Abundance of neutrophils in the subcorneal blister and psoriasiform acanthosis differentiate this case of subcorneal pustular dermatosis (Sneddon-Wilkinson disease) from impetigo.



## KEY FACTS

## TERMINOLOGY

- Deep, suppurative nonfollicular infection of skin or deeper soft tissues caused by number of different infectious organisms

## CLINICAL ISSUES

- Expanding, spreading area of erythema that is usually accompanied by edema, warmth, tenderness, and pain
  - Mild systemic symptoms, including fever and chills may also be associated
- Erysipelas presents as sharply demarcated red plaques with elevated border on face, most commonly due to *Streptococcus pyogenes*
- Erysipeloid (rare) presents as red to purple macules on exposed areas of arms, hands, or fingers

## MICROSCOPIC

- Often marked dermal and subepidermal edema

- Vascular and lymphatic dilatation are also almost always present
- Diffuse and dense neutrophilic infiltrate is often seen beneath edema
  - Neutrophilic infiltrate can be perivascular in location
  - Neutrophils can occasionally involve subcutaneous fat as well
- Older lesions
  - Often show granulation tissue beneath subepidermal edema
  - Milder dermal inflammatory infiltrate with lymphocytes and histiocytes replacing neutrophils

## TOP DIFFERENTIAL DIAGNOSES

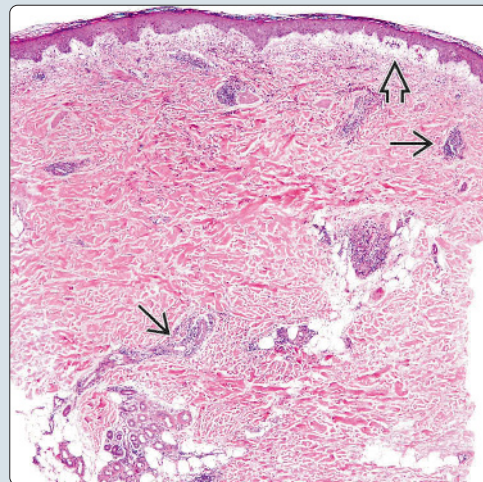
- Urticaria
- Sweet syndrome
- Arthropod bite reaction

Edema, Erythema, Redness, and Bullae Formation

(Left) Cellulitis of the leg shows edema, erythema, redness, and bullae formation, all of which are often seen with *Staphylococcus aureus* infection. (Right) Low-power view of cellulitis demonstrates a superficial and deep perivascular inflammatory infiltrate with subepidermal edema and lymphatic dilatation (not seen).

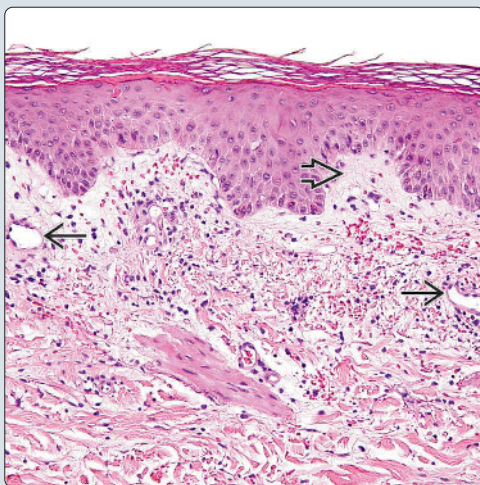


Superficial and Deep Perivascular Infiltrate With Subepidermal Edema

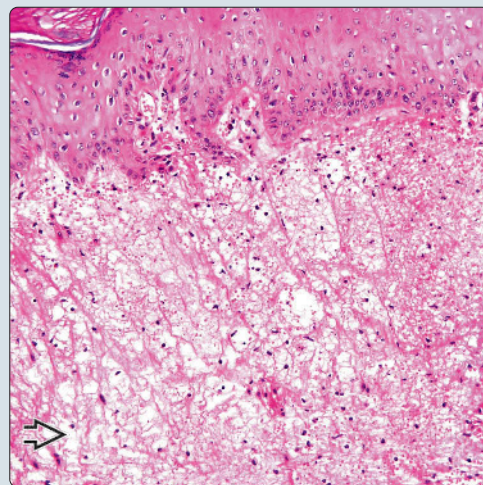


Subepidermal Edema and Lymphatic Dilatation

(Left) High-power view of cellulitis demonstrates subepidermal edema and lymphatic dilatation. The dermal inflammation is milder than normal in this case. (Right) An older lesion of cellulitis demonstrates massive subepidermal edema with a very sparse inflammatory infiltrate associated.



Older Lesion With Massive Subepidermal Edema





**TERMINOLOGY****Synonyms**

- Deep pyogenic infection, infectious cellulitis
- Often synonymous with deep pyogenic infections, which includes entities such as
  - Erysipelas, erysipeloid, blistering distal dactylitis, necrotizing fasciitis (up to 50% mortality)

**Definitions**

- Deep, suppurative nonfollicular infection of skin or deeper soft tissues caused by number of different infectious organisms
  - *Staphylococcus aureus* or group A  $\beta$ -hemolytic streptococci (*Streptococcus pyogenes*)
  - If no bacteria identified by culture, then immunosuppression almost always present

**ETIOLOGY/PATHOGENESIS****Infectious Agents**

- *S. aureus* and group A  $\beta$ -hemolytic streptococci (*S. pyogenes*) are most common causes
  - Breach in skin integrity often serves as portal of entry for these bacteria
    - Trauma, surgical incisions, foreign bodies, underlying dermatosis, etc. all potential causes
    - Interdigital tinea pedis may be portal of entry, especially in diabetics, and should be treated
  - Lack of obvious site of trauma does not rule out diagnosis
- In erysipeloid, bacteria *Erysipelothrix rhusiopathiae* is cause
  - Abrasions on hands of handlers of fish, meat, or poultry create portal of entry

**CLINICAL ISSUES****Site**

- Children
  - Head and neck are most commonly involved areas
- Adults
  - Lower extremities are most commonly involved
    - Especially common, chronic, and difficult to treat with vascular or lymphatic compromise
    - Commonly confused clinically with thrombophlebitis

**Presentation**

- Expanding, spreading area of erythema that is usually accompanied by edema, warmth, tenderness, and pain
  - Mild systemic symptoms, including fever and chills may also be associated
- In elderly, obtundation can be presenting sign
- Erysipelas presents as sharply demarcated red plaques with elevated border on face, most commonly due to *S. pyogenes*
- Erysipeloid (rare) presents as red to purple macules on exposed areas of arms, hands, or fingers
- Blistering distal dactylitis presents as tense, erythematous bullae on distal fingers or thumb of children and adolescents

**Treatment**

- Oral or intravenous antibiotics that are effective against group A streptococci and *S. aureus*
  - If suspected, MRSA should be covered also
  - For recurrent disease of lower legs with vascular compromise, treatment for months or years is option

**Prognosis**

- Excellent but consider hospitalization to monitor therapy if diabetic, compromised circulation of lower extremity, or immunosuppression
  - Sepsis is complication that can be life threatening if therapy not begun in time

**MICROSCOPIC****Histologic Features**

- Often marked dermal and subepidermal edema
- Vascular and lymphatic dilatation are also almost always present
- Diffuse and dense neutrophilic infiltrate is often seen beneath edema
  - Neutrophilic infiltrate can be perivascular in location
  - Neutrophils can occasionally involve subcutaneous fat as well
- Older lesions
  - Often show granulation tissue beneath subepidermal edema
  - Milder dermal inflammatory infiltrate with lymphocytes and histiocytes replacing neutrophils
- Vesicles and bullae seen clinically often histologically demonstrate subepidermal vesiculation with extensive papillary edema
- Hemorrhagic cellulitis can show
  - Necrotizing vasculitis with necrotic keratinocytes and numerous bacteria

**ANCILLARY TESTS****Histochemistry**

- Gram or Giemsa stain can rarely highlight streptococci in tissue and within lymphatics

**DIFFERENTIAL DIAGNOSIS****Urticaria**

- Much milder dermal and perivascular inflammatory infiltrate

**Sweet Syndrome**

- Typically denser neutrophilic inflammatory infiltrate and classic clinical presentation with fever and painful plaques

**Arthropod Bite Reaction**

- Similar histopathologic pattern, but interstitial eosinophils almost invariably present

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## Necrotizing Fasciitis

## KEY FACTS

## TERMINOLOGY

- Life-threatening deep, acute, aggressive bacterial (or rarely fungal) infection of deep soft tissue, including fascia

## ETIOLOGY/PATHOGENESIS

- Group A  $\beta$ -hemolytic streptococcal infection (*Streptococcus pyogenes*) is most common; more cases now polymicrobial

## CLINICAL ISSUES

- Clues to clinical diagnosis include
  - Pain out of proportion to physical exam, hemorrhagic bullae, and vital sign abnormalities

## MICROSCOPIC

- Often subepidermal edema
- Necrosis is invariably present and usually involves epidermis, dermis, and upper portion of subcutis
- Intense mixed inflammatory infiltrate usually admixed with numerous bacteria in dermis, subcutaneous tissue, and in viable areas bordering areas of necrosis

- Septic vasculitis with perivascular inflammation, fibrinoid necrosis, and sometimes thrombi in vessels





## ANCILLARY TESTS

- Frozen sections
  - Biopsy must be down to fascial level
- Finger test
- Culture
- Gram or GMS/PAS stain
- Tissue oxygen saturation by near-infrared spectroscopy

## TOP DIFFERENTIAL DIAGNOSES

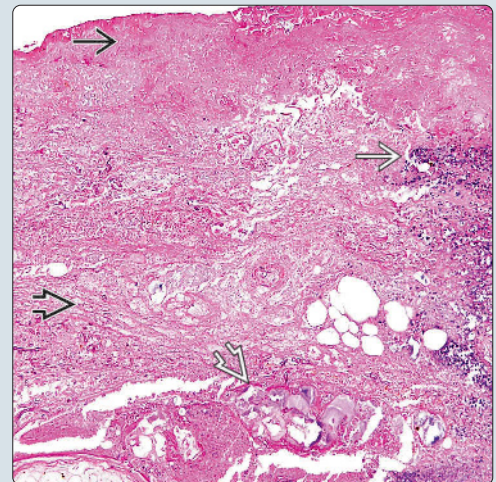
- Cellulitis or erysipelas
  - No fascial involvement on biopsy
- Pyoderma gangrenosum (PG)
  - Epidermal necrosis and deep ulcer is focal
- Sweet syndrome (SS)
  - Dermal neutrophilic infiltrate is typically sheet-like

Swollen, Tender Hand With Pain Out of Proportion to Physical Exam




(Left) A swollen, tender, and erythematous hand with pain out of proportion to physical exam should raise suspicion of necrotizing fasciitis (NF). Aggressive debridement and sometimes limb amputation may be necessary. (Courtesy C. Rhodes, MD.) (Right) NF often shows areas of necrosis involving the epidermis , portions of the superficial and deep dermis , and subcutaneous tissue . Inflammation  is typically in viable areas bordering necrotic tissue.

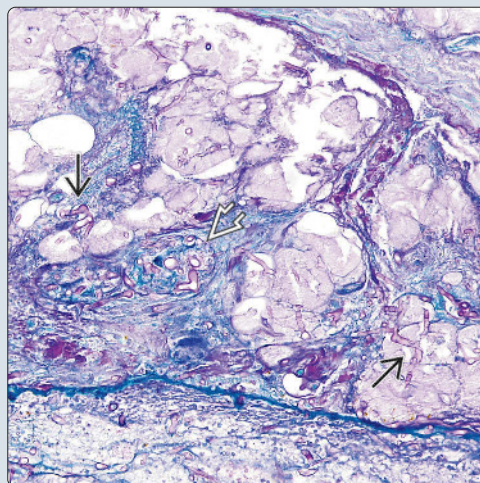


Cutaneous Necrosis Extending to Subcutis

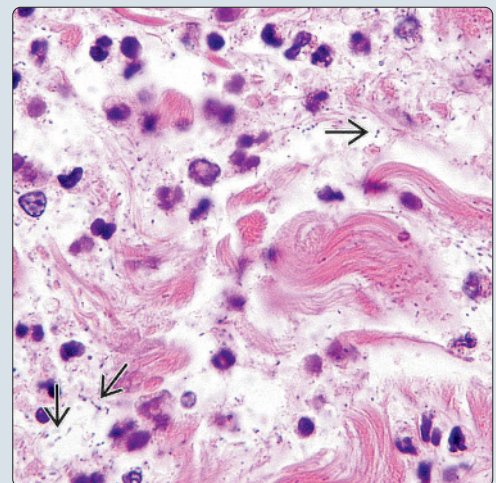


Mucor (Fungal) Necrotizing Fasciitis

(Left) In this case of NF, *Mucor* spp.  with right angle branching were identified on H&E and highlighted with a PAS stain invading deep subcutaneous tissue. Note the characteristic vascular invasion . (Courtesy M. Morgan, MD.) (Right) Although stains are often helpful, organisms often can be seen on H&E alone as in this rare case of pneumococcal NF with numerous discernible lancet-shaped diplococci . (Courtesy K. Duffy, MD.)



Pneumococcal (Bacterial) Necrotizing Fasciitis





## TERMINOLOGY

### Abbreviations

- Necrotizing fasciitis (NF)

### Synonyms

- Fournier gangrene (genital/groin), Meleney ulcer (historical), "flesh-eating bacteria"

### Definitions

- Life-threatening deep, acute, aggressive bacterial (or fungal) infection of deep soft tissue and fascia

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- Group A  $\beta$ -hemolytic strep (*Streptococcus pyogenes*) most common, but often polymicrobial
- Community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) also causative
- Other causative agents include
  - *Vibrio vulnificus*, *Aeromonas hydrophila*, and Enterobacteriaceae (*Escherichia coli*, *Pseudomonas* spp., and *Klebsiella* spp.)

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - 0.40 cases per 100,000 people per year
  - Estimated 500-1,000 cases per year in USA

### Site

- Abdomen, perineum, and extremities most common

### Presentation

- Often nonspecific signs in early stages can mimic cellulitis or erysipelas
  - Tenderness, swelling, erythema, pain
- Clues to clinical diagnosis include
  - Pain out of proportion to physical exam, hemorrhagic bullae, crepitus, and vital sign abnormalities
- Erythematous areas can rapidly become swollen and cyanotic, then gangrenous in  $\leq 5$  days
- Fever, malaise, and altered sensorium may be present

### Laboratory Tests

- Lactate dehydrogenase very elevated

### Treatment

- Broad spectrum IV antibiotics given emergently
- Change to specific antibiotics when culture and sensitivities evaluated
- Emergency aggressive surgical debridement or amputation can be curative
  - Often necessary to repeat

### Prognosis

- 25-50% mortality, which improves if therapy given emergently
- *Vibrio* or *Aeromonas* associated with higher mortality

## MICROSCOPIC

### Histologic Features

- Often subepidermal edema
- Necrosis is invariably present and usually involves epidermis, dermis, and upper portion of subcutis
- Intense mixed inflammatory infiltrate usually admixed with numerous bacteria in dermis, subcutaneous tissue, and in viable areas bordering areas of necrosis
- Septic vasculitis with perivascular inflammation, fibrinoid necrosis, and sometimes thrombi in vessels

## ANCILLARY TESTS

### Frozen Sections

- Biopsy must be down to fascial level
- Very rapid way to diagnose NF

### Finger Test

- Finger or hemostat is placed in 2-cm vertical incision in normal skin down to junction of subcutaneous tissue and deep fascia
  - If subcutaneous tissue is easily dissected off fascia, or "dishwater pus" is expelled, test is positive
  - Pathognomonic for NF if positive

### Culture

- Can help identify causative organisms and help guide antimicrobial therapy
- Rapid streptococcal screen may be helpful to identify  $\beta$ -hemolytic *Streptococcus* (most common organism)

### Gram or Other Special Stains

- Can be used to help identify organisms but is not as sensitive or specific as culture

### Tissue Oxygen Saturation by Near-Infrared Spectroscopy

- High specificity and sensitivity for differentiating NF from more benign entities

## DIFFERENTIAL DIAGNOSIS

### Cellulitis or Erysipelas

- Early NF and cellulitis often indistinguishable
- No fascial involvement on biopsy
- Clinically, NF is more painful, gangrenous earlier, and often crepitant

### Pyoderma Gangrenosum

- Classic clinical lesion has rolled or undermined edges
- Epidermal necrosis and deep ulcer is focal

### Sweet Syndrome

- Clinically presents with painful plaques and fever
- Dermal neutrophilic infiltrate is typically sheet-like

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1. Alayed KA et al: Red Flags For Necrotizing Fasciitis: A Case Control Study. *Int J Infect Dis.* 36:15-20, 2015
2. Khamnuan P et al: Necrotizing fasciitis: epidemiology and clinical predictors for amputation. *Int J Gen Med.* 8:195-202, 2015
3. Umbert IJ et al: Necrotizing fasciitis: a clinical, microbiologic, and histopathologic study of 14 patients. *J Am Acad Dermatol.* 20(5 Pt 1):774-81, 1989

# Ecthyma Gangrenosum

## KEY FACTS

### TERMINOLOGY

- Sepsis (classically with *Pseudomonas aeruginosa*) with skin involvement
  - Other bacterial species have been implicated

### CLINICAL ISSUES

- Single or multiple painful lesions in immunocompromised patients
- Sepsis common, but not absolute
- Symptoms of underlying infection
  - Fever, malaise, diaphoresis, etc.
- Clinical time course
  - Red macule that develops vesicles
  - Infiltration by neutrophils transforms vesicles into pustules
  - Necrosis develops with ulceration and eschar formation
- Most common sites
  - Buttocks, perineum, genitalia, extremities
- Age

- May affect patients of any age
- Sex
  - No gender predilection

### MICROSCOPIC

- Epidermal and dermal necrosis
- Ulceration with serum crust
- Neutrophil and lymphocytic infiltrate
- Numerous bacteria in dermis
- Vessel thrombosis with vasculitis

### TOP DIFFERENTIAL DIAGNOSES

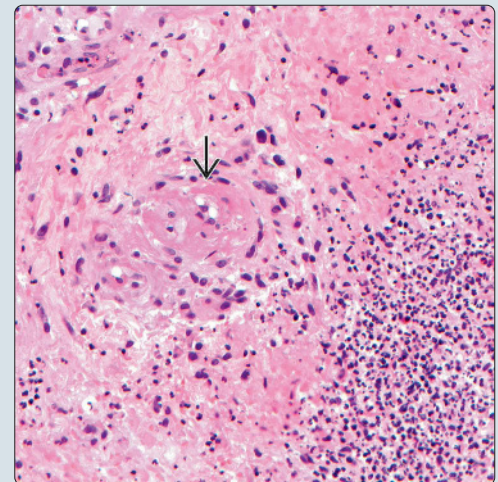
- Purpura fulminans
- Septic vasculitis
- Ecthyma
- Toxic epidermal necrolysis
- Atrophie blanche

**Gangrenous Necrosis on Erythematous Base**

(Left) This is ecthyma gangrenosum over the toe of a patient with pseudomonal sepsis. Black gangrenous changes [X] are seen on a red indurated base [X]. (Right) This vessel is occluded by a thrombus [X]. Necrosis of the surrounding tissue has begun and neutrophils are infiltrating to the damaged tissue.

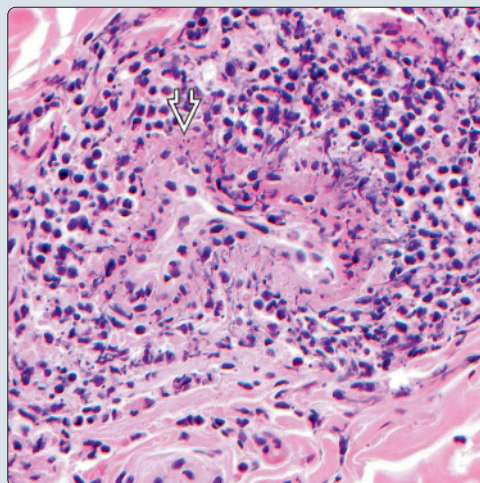


**Thrombus With Acute Inflammation**

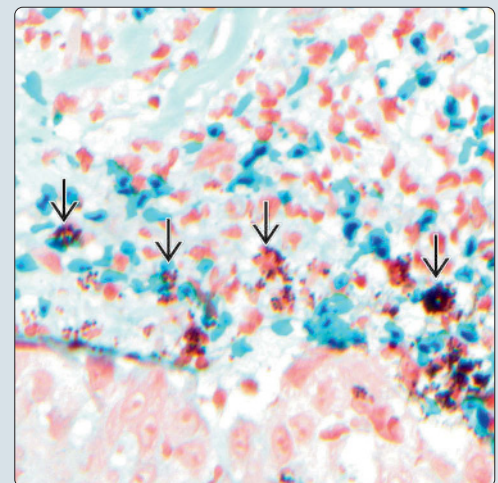


**Neutrophilic Vasculitis**

(Left) Vasculitis is a feature in many cases. Neutrophils are invading the wall of this vessel with subsequent fibrinoid necrosis [X] of the vessel wall. (Right) A tissue Gram stain will help identify bacteria [X]. In this case, the causative organisms were gram-positive cocci.



**Gram Stain**





## TERMINOLOGY

### Definitions

- Sepsis (classically with *Pseudomonas aeruginosa*) with skin involvement
  - Many other bacterial species have been implicated

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Arises in ~ 10% of patients with *P. aeruginosa* sepsis
- Age
  - May affect patients of any age
- Sex
  - No gender predilection

### Site

- Buttocks, perineum, genitalia, extremities

### Presentation

- May present as single or multiple lesions
- Most common in immunocompromised patients
- Sepsis common, but not absolute
- Symptoms of underlying infection
  - Fever, malaise, diaphoresis, etc.

### Natural History

- Sequence of tissue manifestations due to ischemia from vascular thromboemboli
  - Initially red, macular lesion
  - As ischemia continues, vesicles appear
  - Infiltration by neutrophils transforms vesicles into pustules
  - With prolonged tissue ischemia, necrosis ensues
    - Ulceration ± black eschar
    - Erythematous borders with intact tissue
- ± pain

### Treatment

- Drugs
  - Antibiotics, improvement of immunosuppression

### Prognosis

- Dependent on treatment of underlying sepsis

## MICROSCOPIC

### Histologic Features

- Epidermal and dermal necrosis
- Ulceration with serum crust
- Neutrophil and lymphocytic infiltrate
- Numerous bacteria in dermis
  - Usually gram-negative bacilli
- Vessel thrombosis with vasculitis

## ANCILLARY TESTS

### Histochemistry

- Gram stain
- Will identify gram-positive or gram-negative organisms

### PCR

- Available to speciate common bacteria and fungi
- Rapid turnaround time

### Microbiology

- Culture
  - Wound or blood culture is gold standard
  - Collect specimen before treatment, if feasible

## DIFFERENTIAL DIAGNOSIS

### Purpura Fulminans

- Clinical
  - Primarily in childhood
  - Associated with disseminated intravascular coagulation
  - Erythematous macules that develop purpura and subsequent necrosis
  - Causative organisms
    - *Meningococci*, *Streptococcus* spp., *Staphylococcus* spp.
- Histopathology
  - Fibrin thrombi in small vessels
  - No vasculitis and minimal inflammation
  - Dermal and epidermal necrosis
    - Vesicles &/or bullae may form

### Septic Vasculitis

- Clinical
  - Associated with sepsis, infective endocarditis, and secondary syphilis
  - Causative organisms
    - *Meningococci*, *Gonococci*, *Pseudomonas* spp., *Streptococcus* spp., *Staphylococcus* spp.
- Histopathology
  - Involved larger vessels and arterioles
  - Thrombosis of vessels
  - Fibrinoid necrosis of vessel walls (vasculitis)
  - Neutrophils in and around vessels
  - ± leukocytoclasia
  - Necrosis and pustule formation

### Ecthyma

- Well-demarcated ulcers
  - Seen with highly virulent strains of *Streptococcus pyogenes*

### Toxic Epidermal Necrolysis

- Full thickness epidermal necrosis
- Bullae formation with en masse skin sloughing

### Atrophie Blanche

- Telangiectatic papules and plaques with purpura
  - Ulcerations that heal with scarring
- Fibrinoid necrosis of dermal vessels with fibrin thrombi
- Lymphocytes and relatively sparse neutrophils

## SELECTED REFERENCES

1. Vaiman M et al: Ecthyma gangrenosum versus ecthyma-like lesions: should we separate these conditions? *Acta Dermatovenereol Alp Pannonica Adriat.* 24(4):69-72, 2015
2. Yan W et al: Ecthyma gangrenosum and multiple nodules: cutaneous manifestations of *Pseudomonas aeruginosa* sepsis in a previously healthy infant. *Pediatr Dermatol.* 28(2):204-5, 2011

# Staphylococcal Scalded Skin Syndrome

## KEY FACTS

### TERMINOLOGY

- Pemphigus neonatorum, Ritter disease
- Blistering skin disease characterized by extremely tender flaccid blisters that develop on frictional and flexural skin surfaces secondary to release of exfoliatin A and B from certain strains of *Staphylococcus aureus*

### ETIOLOGY/PATHOGENESIS

- These toxins (proteases) cleave desmoglein-1 and cause separation of stratum granulosum and spinosum layers

### CLINICAL ISSUES

- Typically affects infants and children 6 years and under
- Usually involves face, neck, and trunk
- Sudden onset of extreme skin tenderness, burning, and faint macular, red scarlatiniform eruption
- Skin on frictional and flexor surfaces develops large, easily ruptured flaccid bullae that desquamate and form large erosions

- Nikolsky sign (skin peels on gentle pressure) is positive
  - No involvement of mucous membranes (vs. Stevens-Johnson syndrome)

### MICROSCOPIC

- Superficial subcorneal splitting of epidermis at granular layer
- Sparse, polymorphous inflammation in dermis usually seen
- Rare acantholytic cells or sparse neutrophils may be seen within blister (if intact)

### ANCILLARY TESTS

- Immunofluorescence
  - Negative

### TOP DIFFERENTIAL DIAGNOSES

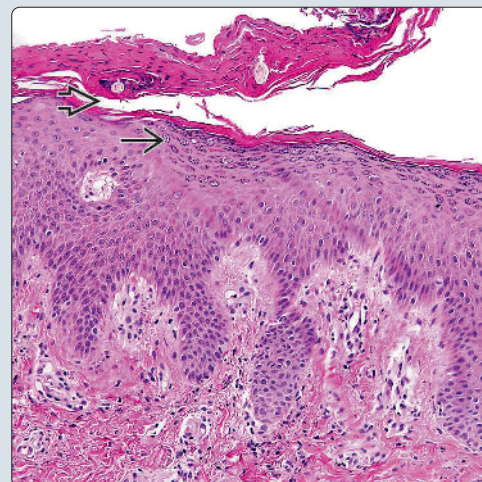
- Bullous impetigo
- Pemphigus foliaceus
- Toxic epidermal necrolysis

### Superficial Erosions

(Left) Clinically, staphylococcal scalded skin syndrome (SSSS) shows superficial erosions over the arm with a positive Nikolsky sign. Although more common in children, SSSS can happen in adults, and a delay in diagnosis can lead to death. (Right) H&E shows classic SSSS demonstrating a subcorneal splitting of the epidermis above the granular layer. Note the absence of inflammatory cells in the blister. (Courtesy C. Coffin, MD.)

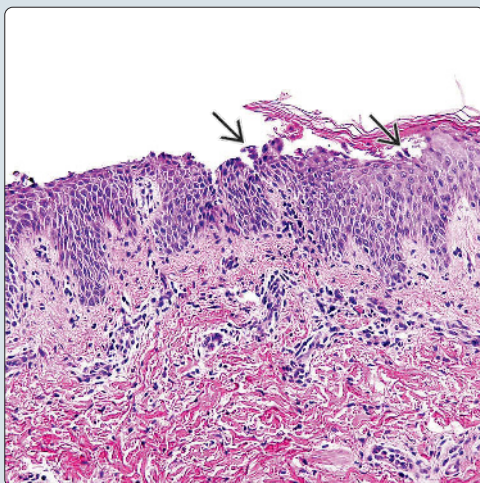


### Sterile Subcorneal Separation

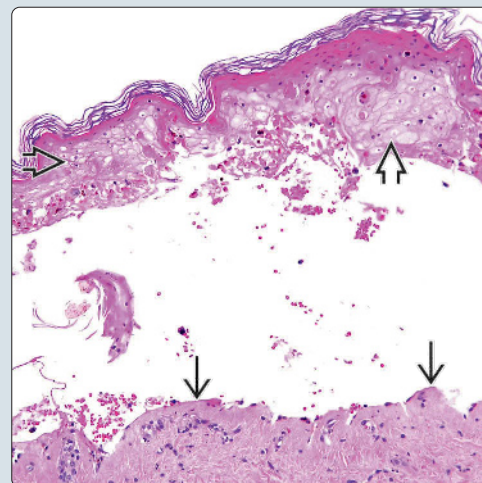


### May Have Acantholysis

(Left) SSSS demonstrates subcorneal (intraepidermal) splitting. Note there are a few acantholytic cells present. (Courtesy H. Zhou, MD.) (Right) Although a difficult differential diagnosis clinically, toxic epidermal necrolysis can easily be distinguished from SSSS due to a deeper (subepidermal) cell-poor blister and full thickness epidermal necrosis.



### Toxic Epidermal Necrolysis





## TERMINOLOGY

### Abbreviations

- Staphylococcal scalded skin syndrome (SSSS)

### Synonyms

- Pemphigus neonatorum, Ritter disease

### Definitions

- Blistering skin disease characterized by extremely tender flaccid blisters that develop on frictional and flexural skin surfaces secondary to release of exfoliatin A and B from certain strains of *Staphylococcus aureus*

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- Some strains of *S. aureus* produce epidermolytic exotoxins (exfoliatin A and B)
  - These toxins (proteases) cleave desmoglein-1 and cause separation of stratum granulosum and spinosum layers
- Toxins (exfoliatin A and B) are produced from staphylococcal infections at distant site (often extracutaneous) and spread hematogenously (vs. bullous impetigo)
  - Pharyngitis, conjunctivitis, and rhinitis are common infections, rarely septicemia

## CLINICAL ISSUES

### Epidemiology

- Age
  - Typically affects infants and children 6 years and under
  - Can affect neonates rarely (Ritter disease)
  - Rarely affects adults who are often immunosuppressed, have chronic illness, or are renal insufficient

### Site

- Usually involves face, neck, and trunk
- No involvement of mucous membranes (vs. Stevens-Johnson syndrome)

### Presentation

- Sudden onset of fever, extreme skin tenderness, burning, and faint macular, red scarlatiniform eruption
- Over next 48 hours, evolves to confluent deep erythema with edema
  - Skin on frictional and flexor surfaces develops large, easily ruptured flaccid bullae that desquamate and form large erosions
  - Nikolsky sign (skin peels on gentle pressure) is positive

### Treatment

- In both adults and children, antistaphylococcal antibiotics are indicated

### Prognosis

- Generally good for children
  - Typically resolves spontaneously over several days
  - Rare cases of death in neonates
- In adults, fatal septicemia can occur

## MICROSCOPIC

### Histologic Features

- Superficial subcorneal splitting of epidermis at granular layer
- Sparse to absent polymorphous inflammation in dermis usually seen
- Rare acantholytic cells or sparse neutrophils may be seen within blister (if intact)

## ANCILLARY TESTS

### Frozen Sections

- Can be used to quickly differentiate SSSS from toxic epidermal necrolysis (TEN)
  - TEN shows subepidermal blister with fully necrotic epidermis
  - SSSS shows epidermal splitting at granular layer

### Immunofluorescence

- Negative (vs. pemphigus foliaceus)

## DIFFERENTIAL DIAGNOSIS

### Bullous Impetigo

- Epidermal split is in granular layer as well
- Involves direct infection of skin from staphylococcal spp. resulting in localized release of toxins (vs. SSSS)
- Mild to moderate polymorphous dermal inflammatory infiltrate (vs. sparse to absent in SSSS)
- Subcorneal blister often contains more neutrophils, and some gram-positive cocci can usually be seen
- Blisters are culture positive (vs. SSSS) due to localized, direct infection with staphylococcal spp.

### Toxic Epidermal Necrolysis

- Extensive, deeper subepidermal (vs. granular) blister at basement membrane
- Full-thickness epidermal necrosis
- Mild superficial perivascular lymphocytic inflammatory infiltrate
- Rare in children
- Mucosal involvement common (vs. SSSS)

### Pemphigus Foliaceus

- Typically affects middle-aged individuals
- Dermal inflammatory infiltrate generally heavier
- Increased IgG desmoglein-1 antibodies can be demonstrated in serum
- Immunofluorescence is positive (vs. SSSS)
  - Direct immunofluorescence of perilesional skin shows intercellular IgG in epidermal squamous cells
    - Complement is also often positive in same pattern

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1. Saida K et al: Exfoliative toxin A staphylococcal scalded skin syndrome in preterm infants. *Eur J Pediatr.* 174(4):551-5, 2015
2. Handler MZ et al: Staphylococcal scalded skin syndrome: diagnosis and management in children and adults. *J Eur Acad Dermatol Venereol.* 28(11):1418-23, 2014
3. Paranthaman K et al: Nosocomial outbreak of staphylococcal scalded skin syndrome in neonates in England, December 2012 to March 2013. *Euro Surveill.* 19(33), 2014

## KEY FACTS

### TERMINOLOGY

- Infectious multisystemic disease caused by spirochete *Borrelia burgdorferi* (sensu lato)

### ETIOLOGY/PATHOGENESIS

- Vector of causative agent (*B. burgdorferi*)
  - *Ixodes dammini* (deer tick): East coast (same as *Ixodes scapularis*)
  - *Ixodes pacificus* (western black-legged tick): West coast
  - *Ixodes ricinus* (castor bean tick): Europe

### CLINICAL ISSUES

- Stage I: Localized disease with erythema chronicum migrans (ECM) in 75% of cases
- Stage II: Disseminated disease with cardiac (atrioventricular block) and neurologic manifestations in most cases
- Stage III: Chronic disease

- Dermatologic conditions include acrodermatitis chronica atrophicans (ACA) (seen mostly in Europe, caused by *Borrelia afzelii*), lymphocytoma cutis, and cutaneous B-cell lymphoma

### MICROSCOPIC

- Histopathologic features depend on stage biopsied
- Presence of plasma cells is clue for spirochetal involvement
- **ECM**
  - Loss of pilosebaceous units is characteristic
  - Superficial and deep, tightly cuffed, perivascular infiltrate
- **ACA**
  - Dense, patchy, superficial and deep infiltrate
  - Dilated and ectatic vessels are characteristic
- **Lymphocytoma cutis (pseudolymphoma)**
  - Characteristically shows dense, mixed diffuse dermal infiltrate
  - Polyclonal, mature lymphocytes
  - Reactive germinal centers

### Erythema Chronicum Migrans

(Left) Characteristic clinical appearance of erythema chronicum migrans (ECM) shows an oval, erythematous, solitary "targetoid" patch that is > 5 cm and expands in size over days to weeks. (Right) Clinical changes in acrodermatitis chronica atrophicans (ACA) are seen involving the right knee with violaceous coloration of the skin without scaling.

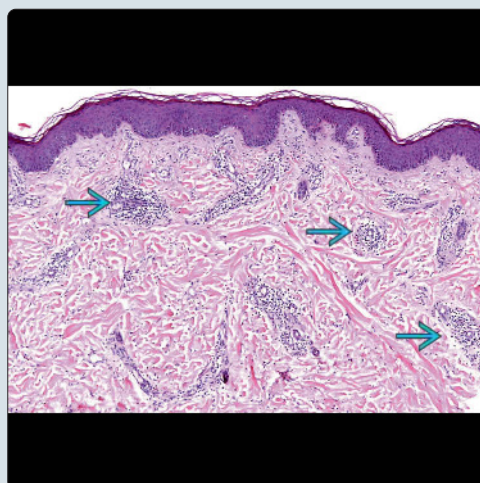


### Acrodermatitis Chronica Atrophicans

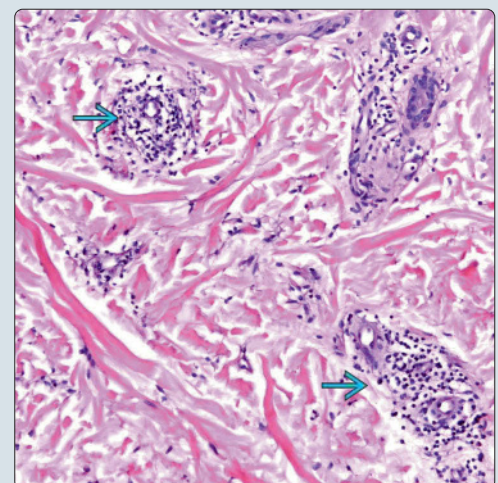


### Perivascular Lymphocytic Infiltrate, Low Power

(Left) Under a normal-appearing epidermis, a lymphocytic perivascular infiltrate is seen in the superficial and mid dermis (magnification 100x). (Right) Higher power image shows perivascular lymphocytic infiltrate lacking any obvious increase in mucin deposition (magnification 200x).



### Perivascular Lymphocytic Infiltrate, High Power





## TERMINOLOGY

### Abbreviations

- Lyme disease (LD)

### Synonyms

- *Borrelia burgdorferi* disease, borreliosis

### Definitions

- Infectious multisystemic disease caused by spirochete *B. burgdorferi* (sensu lato)
- Classic sequence of 3 stages can be observed, and most organ systems of body are affected
  - Chronic disease with involvement of skin, joints, muscles, and nervous system
    - Secondary erythema migrans

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- Vector of causative agent (*B. burgdorferi*)
  - *Ixodes dammini* (deer tick): East coast (same as *Ixodes scapularis*)
  - *Ixodes pacificus* (western black-legged tick): West coast
  - *Ixodes ricinus* (castor bean tick): Europe
- Pathogenic genospecies of *B. burgdorferi* are cause
  - Spain: *Borrelia valaisiana*
  - United States: *B. burgdorferi*
  - Europe: *B. burgdorferi*, *Borrelia afzelii*, and *Borrelia garinii*
- Disease has worldwide prevalence with incidence rates equal between Europe and USA

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - United States in Northeast, Upper Midwest, Coastal Western, and mid-Atlantic
    - CT, NY, RI, NJ, DE, PA, MD, WI, and NH account for over 90% of cases
  - Endemic in areas of Canada, temperate Eurasia, and South America
  - ~ 20,000 cases are reported in USA each year
    - Higher incidence is suspected due to lack of recognition
- Age
  - Affects all ages
  - 2 distinct peaks at 5-9 and 60-70 years

### Presentation

- 3 clinical stages are observed
- Stage I: Localized disease with erythema chronicum migrans (ECM) in 75% of cases
- Stage II: Disseminated disease with cardiac (atrioventricular block) and neurologic manifestations in most cases
- Stage III: Chronic disease
  - Dermatologic conditions include
    - Acrodermatitis chronica atrophicans (ACA): Seen mostly in Europe, caused by *B. afzelii*
    - Lymphocytoma cutis
    - Cutaneous B-cell lymphoma

- Nondermatologic conditions include arthritis, chronic neuropathy, meningoencephalitis, and fibromyalgia-like symptoms

### Laboratory Tests

- Testing for IgG or IgM anti-*Borrelia* antibodies
  - Enzyme-linked immunosorbent assay (ELISA)
    - 30% false-negative rate in early disease (< 6-8 weeks)
  - Immunofluorescence assay (IFA)
  - ELISA and IFA have ~ 90% sensitivity and 70% specificity when at least 1 clinical manifestation is present
- If ELISA or IFA are positive or indeterminate, confirmation is needed
  - Western blot for *Borrelia*

### Treatment

- Drugs
  - Oral and systemic antibiotics (doxycycline in adults and amoxicillin in children)
  - NSAIDs or hydroxychloroquine for arthritis pain

### Prognosis

- Prognosis in stage I and II is favorable
  - Complete resolution in most cases
- Once in stage III, prognosis is poor

### Clinical History

- Outdoor activities &/or tick bite
  - If bite occurs in hard-to-see location, tick bite may not be reported

## MICROSCOPIC

### Histologic Features

- Best location for taking biopsy
  - ECM: Leading edge
  - ACA: Area with most significant inflammatory changes
  - Lymphocytoma cutis: Center
- ECM
  - Epidermal changes vary depending on age of lesion and location of biopsy
    - Normal epidermis without interface alterations or relevant spongiosis can be seen
    - Spongiotic foci and slight epidermal atrophy may be present
- Dermis
  - Loss of pilosebaceous units is characteristic
  - Superficial and deep, tightly cuffed, perivascular infiltrate
  - Lymphocytes, plasma cells, and mast cells
  - Due to central insect bite reaction, some scattered eosinophils can be found in center of lesion
  - Presence of plasma cells is clue for spirochetal involvement
- ACA
  - Epidermis: Acanthosis, parakeratosis, or epidermal atrophy (depending on sequence of disease)
- Dermis
  - Dense, patchy, superficial, and deep infiltrate
  - Lymphocytes, histiocytes, and mast cells
  - Dilated and ectatic vessels are characteristic
  - Mucin deposition may be seen

- Late stages: Epidermal atrophy and dermal sclerosis with loss of elastic fibers
- **Lymphocytoma cutis (pseudolymphoma)**
  - Characteristically shows dense, mixed diffuse dermal infiltrate
  - Polyclonal, mature lymphocytes
  - Reactive germinal centers
  - Main differential is B-cell lymphoma

## ANCILLARY TESTS

### Histochemistry

- Warthin-Starry and modified Steiner silver stains identify spirochetes

### Immunohistochemistry

- Anti-*Treponema pallidum* stain
  - May cross react with some *Borrelia* species and give positive reaction

### PCR

- Direct isolation of *Borrelia* DNA in tissue specimens can be helpful

### Serologic Testing

- 2-tiered system with ELISA or IFA followed by western blot
- Intrathecal anti-*Borrelia* antibodies can be found in patients with neuroborreliosis

## DIFFERENTIAL DIAGNOSIS

### ECM

- LD is most often diagnosed clinically, but differential diagnoses are extensive and may be challenging, in particular due to often uncommon atypical variants of early ECM
- Insect bite
  - Typically wedge-shaped silhouette with eosinophils
  - Multiple, very pruritic, urticarial papules
  - No bull's-eye areas of erythema
- Other cutaneous infections
  - Special stains helpful to identify characteristic organism morphology
  - Often with fever, elevated WBC with neutrophilia, tenderness, and warmth if due to bacteria
  - Elevated vesicular, papular, or oozing border if due to fungus
- Urticaria
  - Perivascular infiltrate often not as prominent
  - Interstitial neutrophils and eosinophils
  - Papillary dermal edema
  - Often multiple, very pruritic, and evanescent
- Erythema multiforme
  - More of clinical differential diagnosis
  - Will show superficial keratinocyte necrosis
  - Vacuolar interface change
  - Multiple, symmetric, bull's-eye oval rings
  - Palmar and mucous membrane lesions are common
  - History of herpes simplex infection or offending drug
- Erythema annulare centrifugum
  - Typically coat-sleeve perivascular lymphocytic infiltrate
  - Few lesions but peripheral scale on outer edge

- Often chronic with no response to systemic antibiotics
- Granuloma annulare
  - Typically has palisaded histiocytes with necrobiosis and mucin deposition
  - Multiple, oval, pink, indurated ovals only 1-2 cm or less
  - Mainly over joints and lasts months to years without treatment
- Erythema infectiosum
  - Mild perivascular lymphocytic infiltrate
  - Serological confirmation of parvovirus B19 infection
  - In infants, multiple pustules  $\leq 1$  cm

### ACA

- Scleroderma/morphea
  - Can mimic late-stage ACA
  - Skin more bound down and may have progressive systemic sclerosis
- Lichen sclerosus et atrophicus
  - Late-stage ACA appears similar
  - Majority of cases in genital area
  - Hyalinization of papillary dermis
- Scleromyxedema
  - Both may have mucin deposition
  - Irregular fibroblast proliferation in scleromyxedema
  - Associated with abnormal immunoglobulins
  - Generalized wide folds of induration with disfigured leonine facies

### Lymphocytoma Cutis

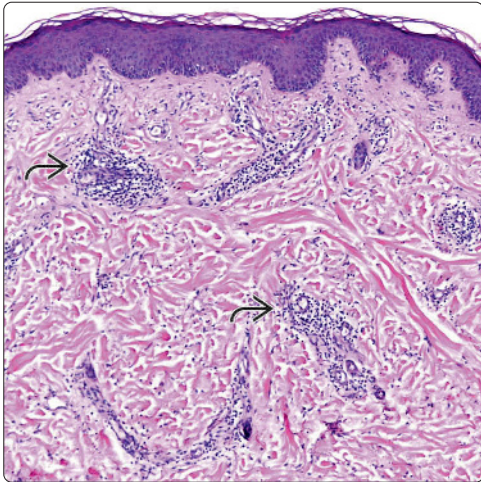
- B-cell lymphoma
  - Kappa or lambda restricted staining of B cells would favor clonal B-cell process
    - Mixture of kappa and lambda staining would favor lymphocytoma cutis
  - CD3 and CD20 stains will show predominance of CD20 staining (monoclonal process)
    - Reactive conditions, such as lymphocytoma cutis, should demonstrate good mixture in staining for both CD3 and CD20 (polyclonal)
  - Mainly histologic diagnosis
- Chronic insect bite reactions
  - Should show good mixture of B (CD20) and T (CD3) cells
  - $\kappa$  and  $\lambda$  staining of B cells should show polyclonality
  - Eosinophils are common
  - Indurated and indents upon pressure from side
  - Occasional history of insect bite

## SELECTED REFERENCES

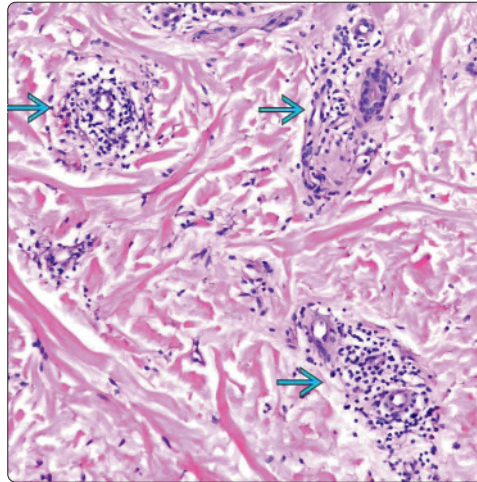
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**Erythema Chronicum Migrans Showing Lymphocytic Infiltrate**

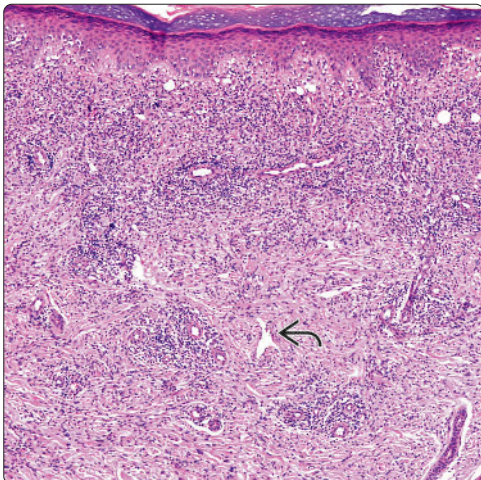


**Erythema Chronicum Migrans With Tight Cuffing of Lymphocytic Infiltrate**

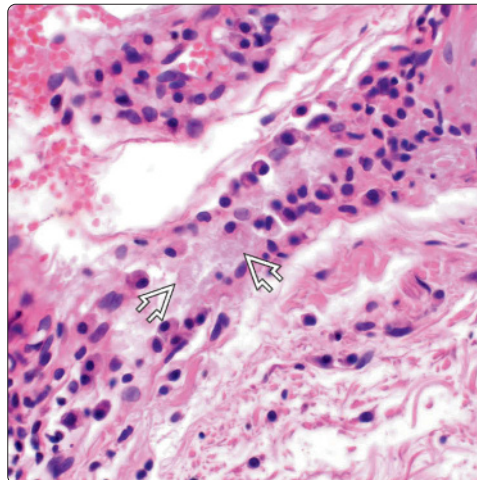


(Left) ECM shows the lymphocytic perivascular infiltrate [1] in the superficial and mid dermis. (Right) ECM characteristically shows a tightly cuffed perivascular lymphocytic infiltrate [2].

**Acrodermatitis Chronica Atrophicans, Low Power**

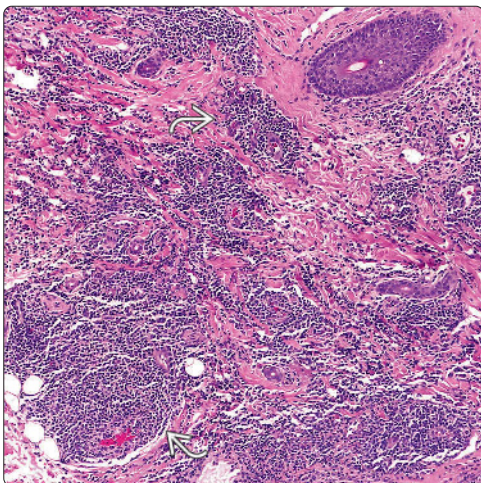


**Acrodermatitis Chronica Atrophicans, High Power**

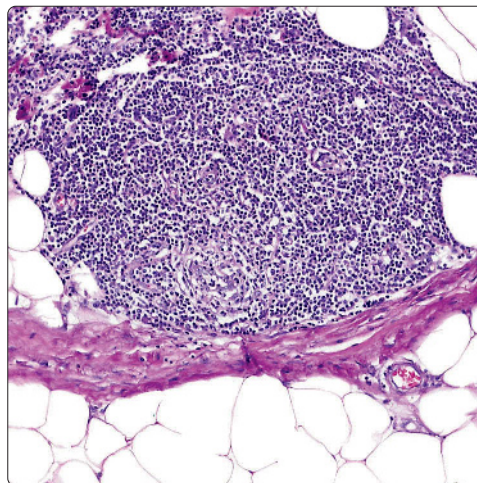


(Left) ACA shows slight acanthosis with a dense, patchy, superficial, and deep infiltrate with dilated and ectatic vessels [1]. (Right) High-power view of ACA shows lymphocytes, histiocytes, plasma cells, and mast cells with some mucin deposition [2] amidst the dense inflammatory infiltrate.

**Lymphocytoma Cutis, Medium Power**



**Lymphocytoma Cutis, High Power**



(Left) Lymphocytoma cutis shows a much more dense, superficial, and deep inflammatory infiltrate [1] that can simulate lymphoma. (Right) High-power view of lymphocytoma cutis shows large lymphoid aggregates sometimes with germinal center formation.



## KEY FACTS

### ETIOLOGY/PATHOGENESIS

- *Mycobacterium tuberculosis* is etiologic agent
- Mechanism of propagation is by direct inoculation, contiguous infection, and hematogenous spread

### CLINICAL ISSUES

- Multibacillary forms
  - Primary inoculation tuberculosis (TB), scrofuloderma, TB periorificialis, acute miliary TB, and gumma
- Paucibacillary forms
  - TB verrucosa cutis, lupus vulgaris, erythema induratum of Bazin, lichen scrofulosorum, papulonecrotic tuberculid, lupus miliaris disseminatum faciei, and granulomatous mastitis

### MICROSCOPIC

- 3 main histological patterns

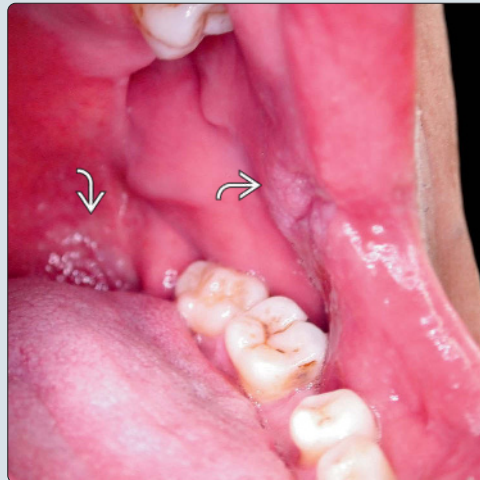
- Superficial tuberculoid granulomatous with pseudoepitheliomatous hyperplasia; granulomas are very close to epidermis
- Deep tuberculoid granulomas without pseudoepitheliomatous hyperplasia
- Superficial and deep tuberculoid granulomas with caseous necrosis without pseudoepitheliomatous hyperplasia

### TOP DIFFERENTIAL DIAGNOSES

- Leprosy
- Leishmaniasis
- Sporotrichosis
- Actinomycosis
- Atypical mycobacterial infections
- Nodular vasculitis

Oral Erosions of Periorificial TB

(Left) Two oral erosions with indurated white borders on the buccal mucosa are indicative of periorificial TB. (Right) Papules, plaques, and an ulcer are shown in a case due to perianal TB.

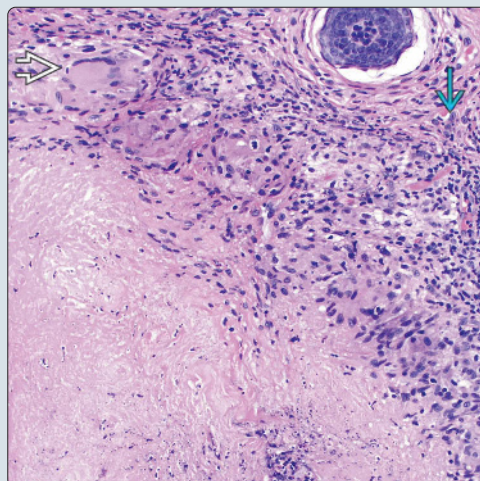


Perianal Cutaneous TB With Ulcer



Tuberculoid Granuloma

(Left) A tuberculoid granuloma is formed by loosely arranged histiocytes (some multinucleate) surrounded by a perimeter of lymphocytes. Necrosis is seen centrally. (Right) Indurated rosy nodule with slight central scale is an example of primary inoculation TB. Posterior cervical lymphadenopathy is seen on the neck.



Primary Inoculation TB





**TERMINOLOGY****Abbreviations**

- Tuberculosis (TB)

**Definitions**

- Cutaneous TB is chronic infectious disease caused by *Mycobacterium tuberculosis*, same bacteria that causes pulmonary TB

**ETIOLOGY/PATHOGENESIS****Environmental Exposure**

- Mechanism of propagation is by direct inoculation, either through contiguous infection and hematogenous dissemination

**CLINICAL ISSUES****Epidemiology**

- Incidence
  - Rare disease
    - Cutaneous disease represents 0.5-1.4% of all TB cases even in endemic countries, such as India, China, South Africa, Peru, and Bolivia

**Presentation**

- Multibacillary forms
  - Primary inoculation TB (tuberculous chancre)
    - Patients are healthcare workers or children with no BCG immunization exposed to *M. tuberculosis* through household member with pulmonary TB
    - Lesions are usually located on face, hands, and feet
    - Lesion is papule or nodule that becomes ulcerated after 2 or 3 weeks of exposure
  - Scrofuloderma
    - Most common form of cutaneous TB in developing countries (patients have pulmonary or pleural TB)
    - Caused by contiguous propagation of bacteria from lymph node or bone
    - Most commonly affected areas are neck, axillae, thorax, and groin
    - Lesion is abscess that becomes ulcer surrounded by keloid tissue with underlying fistulae formation
  - Tuberculosis periorificialis
    - Oral TB is secondary to active pulmonary TB, whereas perineal TB is secondary to intestinal or genitourinary disease
    - Involved areas are buccal mucosa, around anus, vulva, or penis
    - Lesion is painful ulcer with pseudomembranous fibrinous base or, occasionally, plaque similar to those seen in lupus vulgaris or TB verrucosa cutis
  - Acute miliary TB
    - Usually seen in patients with advanced pulmonary or disseminated TB
    - Trunk is most common location
    - Lesions are small macules or papules that become necrotic
  - Gumma
    - Secondary to hematogenous spread of bacteria that remain latent

- Lesions are cold abscesses in extremities or on trunk
- Paucibacillary forms
  - TB verrucosa cutis
    - Caused by reinoculation to *M. tuberculosis* in individual with previous exposure and strong cell-mediated immunity
    - Affects adults and children
    - Lesion is solitary, verrucous plaque on hands or feet
  - Lupus vulgaris
    - Most common form in India and Europe
    - Lesions due to hematogenous spread are found on face, and those located on extremities occur by reinoculation
    - Lesion is red-brown plaque with verrucous border and central atrophy; plaque is result of multiple coalescent papules and has classic apple-jelly appearance
  - Tuberculids: Erythema induratum of Bazin (EIB), lichen scrofulosorum, papulonecrotic tuberculid, lupus miliaris disseminatus faciei, and granulomatous mastitis
    - EIB: Most common form of tuberculid; ulcerated subcutaneous nodules on posterior aspect of legs, more commonly in women
    - Papulonecrotic tuberculid: Lesions are found on extensor areas of extremities but can occur on lower abdomen, trunk, or buttocks; multiple symmetric papules with umbilicated, necrotic center
    - Lichen scrofulosorum: Occurs mostly in children as multiple miniature follicular or perifollicular lichenoid papules; almost always affects trunk
  - 2 controversial diseases; some consider both to be tuberculids
    - Granulomatous mastitis: Unilateral, ulcerated plaques or nodules on breast of female with positive contact of TB; has chronic course
    - Lupus miliaris disseminatus faciei: Multiple necrotic lesions on face (usually around eyelids) that leave varioliform scar

**Laboratory Tests**

- Intradermal reaction to purified protein derivative (PPD) test or Mantoux test
  - > 5 mm in immunocompromised patients, HIV-positive patients, and patients with recent TB contact or x-ray changes consistent with healed TB
  - > 10 mm considered positive in adults and children from endemic areas or in setting of high risk (i.e., laboratory personnel involved with testing of TB)
  - > 15 mm considered positive in immunocompetent individuals with no known risk factor for TB infection
- Interferon gamma release assay measures immune reactivity to *M. tuberculosis*

**Treatment**

- Drugs
  - Standard therapy regiment
    - 2 months of quadruple therapy (isoniazid, rifampicin, pyrazinamide, and ethambutol)
    - Followed by 4 months of isoniazid plus rifampicin
  - Clinical response should be expected by week 4 or 6 of treatment
  - Some cases require longer than 6-month regiment

## MICROSCOPIC

### Histologic Features

- Tuberculoid granuloma: Loose aggregate of histiocytes (some multinucleate) surrounded by mantle of lymphocytes, possibly with central caseation necrosis
- 3 main patterns
  - Superficial tuberculoid granulomas with pseudoepitheliomatous hyperplasia, granulomas localized immediately below epidermis
    - Pattern seen in verrucous TB and lupus vulgaris of extremities
  - Deep tuberculoid granulomas that can show caseous necrosis localized in reticular dermis with normal, ulcerated, or acanthotic epidermis
    - Pattern seen in scrofuloderma
  - Superficial &/or deep tuberculoid granulomas with caseous necrosis (not always present); pseudoepitheliomatous hyperplasia is not present
    - Pattern seen in gummas, tuberculous chancre, TB periorificialis, facial lupus vulgaris, and lupus miliaris disseminatus faciei
- Some important points
  - Scrofuloderma
    - Sometimes epidermis is normal, and base of dermis is ceiling of granulomatous reaction
  - Lupus miliaris disseminatus faciei
    - Perifollicular granulomas, as in rosacea, can be seen
  - EIB
    - Lobular panniculitis, necrosis of fat tissue, vasculitis of small or large vessels, and granulomatous formation
  - Papulonecrotic tuberculid and lichen scrofulosorum
    - Normal or ulcerated epidermis with superficial &/or deep granulomas
- Acid-fast bacilli may be seen within areas of necrosis, and number of bacilli increase in areas of more necrosis
  - Bacilli may be seen on Ziehl-Neelsen, Fite

## ANCILLARY TESTS

### PCR

- Available and allows identification of mycobacterial species

### Genetic Testing

- 16S rRNA gene sequence analysis
  - Currently very expensive but another option for definitive identification of species

### Serologic Testing

- Interferon gamma release assay
  - ELISA-based test that can detect latent disease among patients at increased risk for TB
  - Should not be used alone for diagnosis or exclusion of TB
  - Specific for *M. tuberculosis* and not BCG vaccine (vs. PPD derivative)

### Culture

- Isolation of *M. tuberculosis* in AFB culture media is gold standard
  - Often, AFB stain is done in tandem

### Nucleic Acid Amplification Test

- Available for respiratory specimen testing

- Rapid and specific but not as sensitive as culture

## DIFFERENTIAL DIAGNOSIS

### Other Infectious Entities

- Leishmaniasis
  - When lesions show tuberculoid granulomas (group D of Ridley classification)
  - Demonstration of amastigotes with nucleus and kinetoplast on H&E or with special stains helps differentiate
- Deep fungal infections (especially sporotrichosis)
  - Occasionally *Sporothrix schenckii* can be visualized in skin biopsies; tuberculoid granulomas are very common, sometimes with presence of asteroid bodies
  - Definitive diagnosis requires isolation of fungus in specimen culture
- Actinomycosis
  - Characterized by mixed suppurative granulomatous inflammation and presence of sulfur granules
  - Masses of gram-positive bacteria with branching filaments arranged in radial pattern within granules helps favor actinomycoses
- Atypical mycobacterial infections
  - Suppurative granulomatous reaction is most common pattern
  - Culture, clinical history, &/or molecular tests (i.e., PCR) often necessary to definitively differentiate
  - *Mycobacterium bovis* infection can clinically have lupus vulgaris or scrofuloderma appearance

### Nodular Vasculitis

- Main differential diagnosis of EIB (clinically and histologically identical)
- Related to venous insufficiency
- If patient is from area of high prevalence of TB, has contact with TB or previous TB disease, positive PPD reaction is more likely to be EIB

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**Apple-Jelly Appearance of Facial Lupus Vulgaris**



**Scar After Treatment for Lupus Vulgaris**

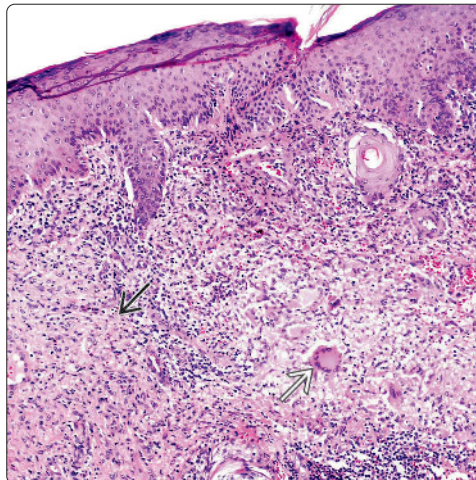


(Left) Classic clinical presentation of facial lupus vulgaris shows an apple-jelly appearance. (Right) A lupus vulgaris patient in remission after treatment has the entire side of her face replaced with a white smooth scar.

**Linear Ulcer of TB Gumma**

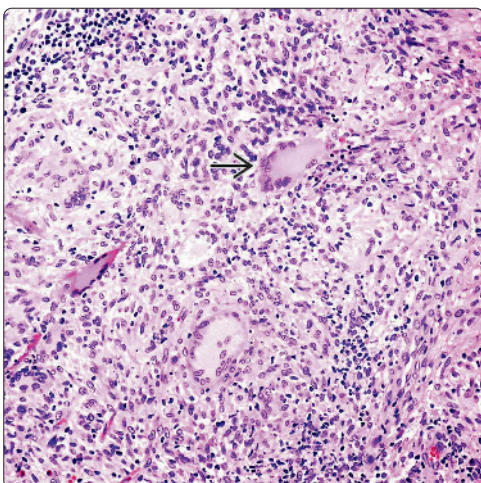


**Tuberculous Granulomas**



(Left) Clinical photograph shows a linear ulcer with a white, central, indented draining scar and surrounding hyperpigmentation secondary to TB gumma. (Right) A biopsy from a case of facial lupus vulgaris demonstrates an acanthotic epidermis, superficial tuberculous granulomas immediately beneath the epidermis, and occasional Langhans giant cells.

**Tuberculoid Granuloma**



**Linear Red Atrophic Scars of Scrofuloderma**



(Left) High-power view of a tuberculoid granuloma shows occasional multinucleated Langhans giant cells. (Right) This case of scrofuloderma shows linear, red, irregularly bordered atrophic scars on the neck and upper chest.

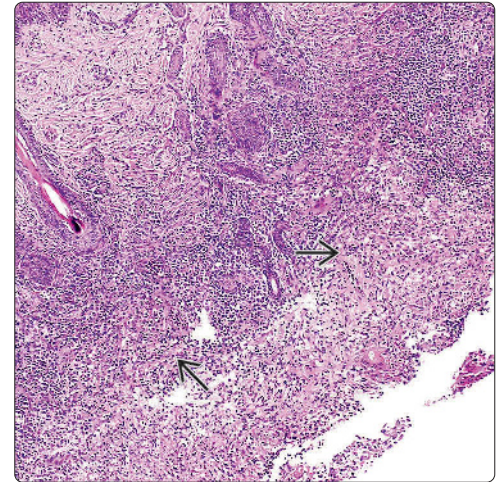


(Left) Another case of scrofuloderma demonstrates linear, irregular scars along the neck. (Right) A biopsy of scrofuloderma shows deep tuberculoid granulomas [X] often with a rim or collar of lymphocytes occupying the deep dermis.

Linear Atrophic Scars

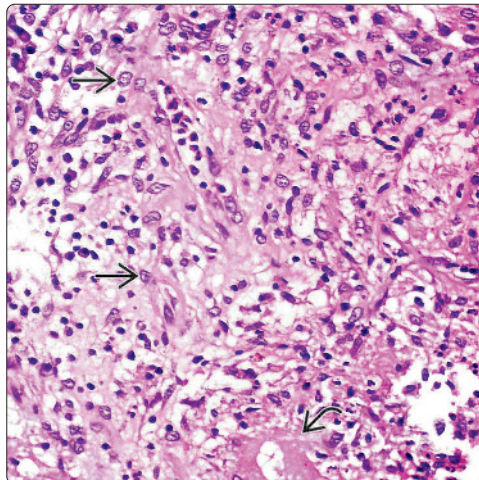


Deep Tuberculoid Granulomas



(Left) High-power view of a characteristic tuberculoid granuloma in the deep dermis demonstrates numerous epithelioid histiocytes [X] surrounding an area of caseous necrosis [X]. (Right) A large verrucous plaque on swollen, discolored skin of the sole is indicative of TB verrucosa cutis.

Tuberculoid Granuloma High Power



Verrucous Plaque of TB Verrucosa Cutis

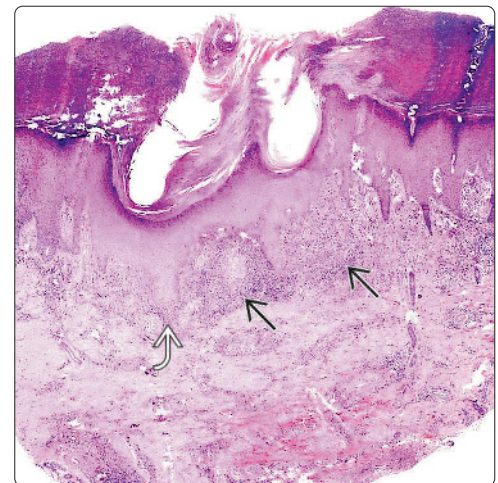


(Left) Lupus vulgaris on the dorsal hand shows a verrucous border of the plaque with central atrophy. (Right) This biopsy from a case of TB verrucosa cutis shows pseudoepitheliomatous hyperplasia [X] with a superficial infiltrate of tuberculous granulomas [X].

Plaque of Lupus Vulgaris

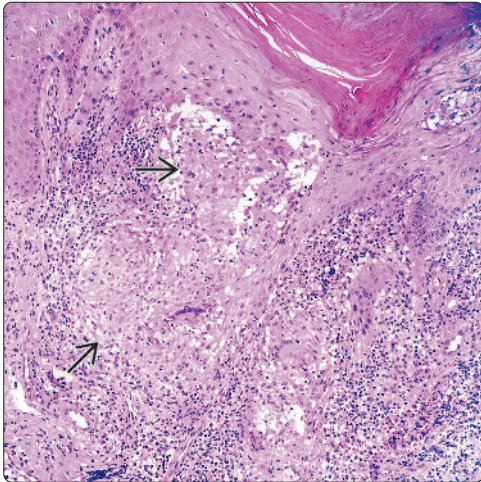


Pseudoepitheliomatous Hyperplasia With Tuberculous Granulomas

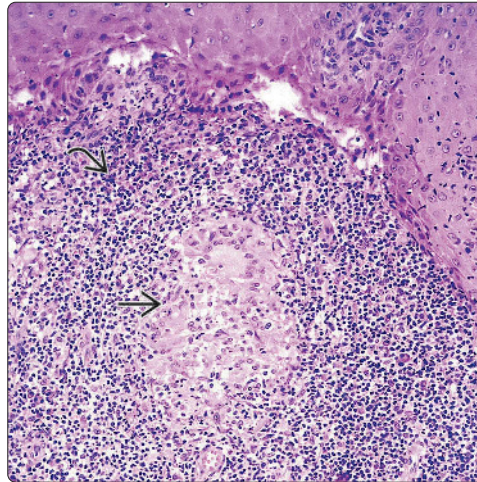







**Superficial Tuberculoid Granulomas**



**Tuberculoid Granuloma Surrounded by Lymphocytes**

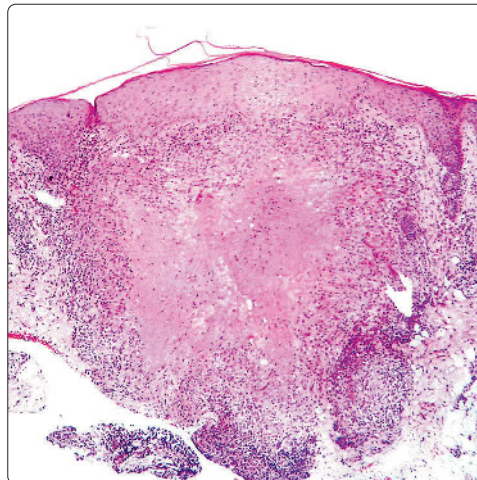


(Left) This biopsy of a case of lupus vulgaris of the extremity demonstrates superficial tuberculoid granulomas  "kissing" the epidermis. (Right) At high power, a superficial tuberculoid granuloma  is shown with surrounding collarette of lymphocytes  immediately beneath the epidermis, as seen in verrucous TB and lupus vulgaris of the extremities.

**Lupus Miliaris Disseminatus Faciei**

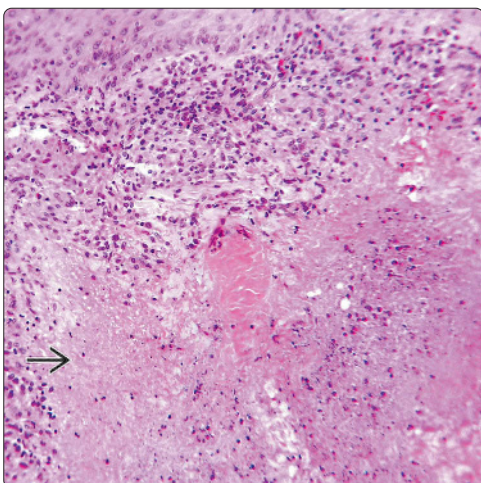


**Large Tuberculoid Granuloma**

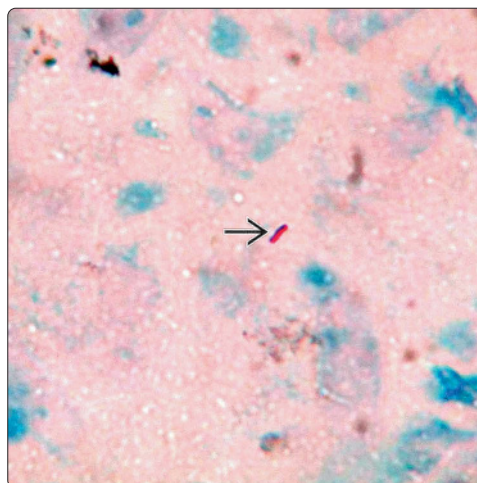




(Left) Papules, plaques, and varioliform scars on the face are typical of lupus miliaris disseminatus faciei. (Right) A biopsy of lupus miliaris disseminatum faciei demonstrates no pseudoepitheliomatous hyperplasia and a superficial and deep large tuberculoid granuloma.

**Caseous Necrosis in Large Tuberculoid Granuloma**



**Red Acid-Fast Bacilli of TB**



(Left) At high power, biopsies of lupus miliaris disseminatum faciei can show tuberculoid granulomas with caseous necrosis . (Right) A Ziehl-Neelsen or acid-fast stain can help identify the acid-fast bacilli of TB by staining them bright red  ("red snappers").

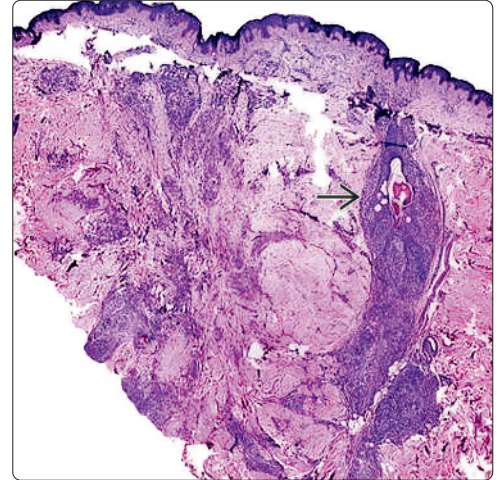


## Papules and Scars of Lupus Miliaris Disseminatus Faciei

(Left) Papules and multiple varioliform scars with palpebral involvement were present in this patient with lupus miliaris disseminatus faciei. (Courtesy Z. Kumakawa, MD.) (Right) This biopsy of lupus miliaris disseminatus faciei shows follicular involvement [2].

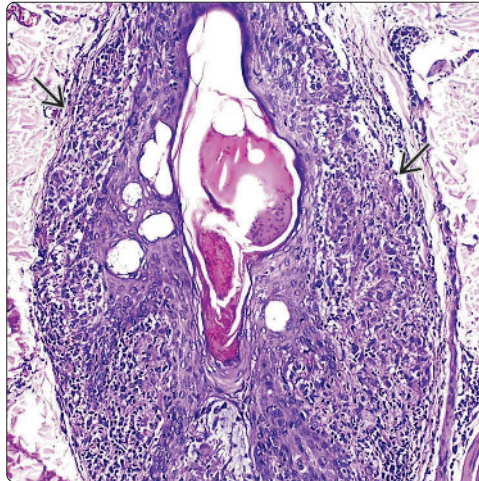


## Follicular Involvement in Lupus Miliaris Disseminatus Faciei



## Perifollicular Tuberculoid Granuloma

(Left) High-power view of a biopsy of lupus miliaris disseminatus faciei shows a perifollicular tuberculoid granuloma [2]. (Right) A case of papulonecrotic tuberculid shows crusted red papules [2] over the upper outer arm of this patient.



## Crusted Red Papules of Papulonecrotic Tuberculid

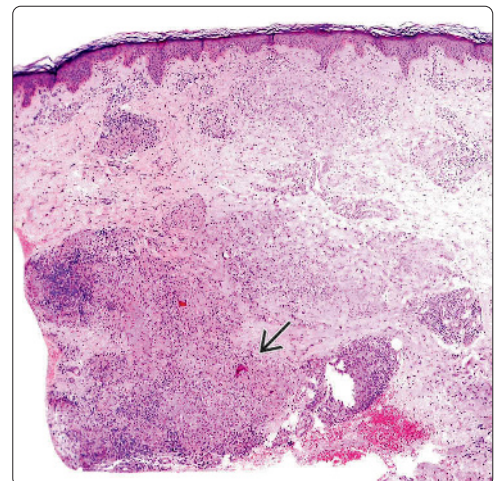


## Erythematous Nodules of Papulonecrotic Tuberculid

(Left) This case of papulonecrotic tuberculid demonstrates erythematous nodules [2] over the elbow of this patient. (Right) A biopsy of papulonecrotic tuberculid shows a normal epidermis with deep granulomas [2].

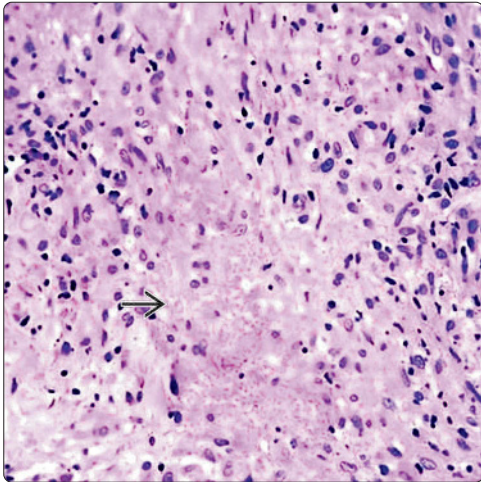


## Deep Granulomas in Papulonecrotic Tuberculid





**Tuberculoid Granuloma With Caseous Necrosis**



**Deep Nodules of Erythema Induratum of Bazin**

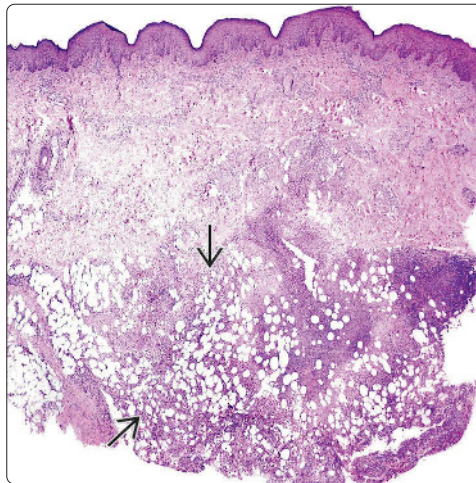


(Left) High-power view of a tuberculoid granuloma shows epithelioid histiocytes surrounding central caseous necrosis [X]. (Right) In this patient with erythema induratum of Bazin, deep nodules with hyperpigmented centers and brown/red borders [X] can be seen over the legs.

**Ulcerated Plaque of Erythema Induratum of Bazin**

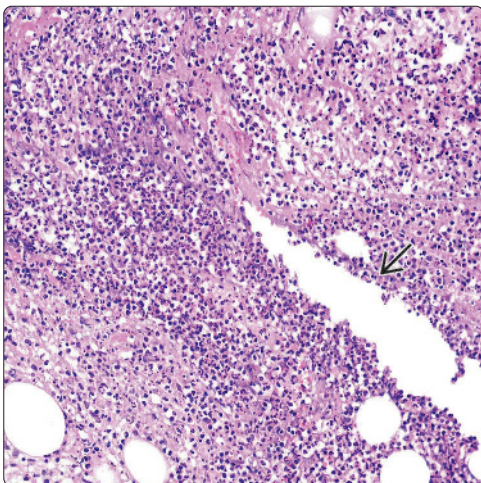


**Lobular Panniculitis of Erythema Induratum of Bazin**

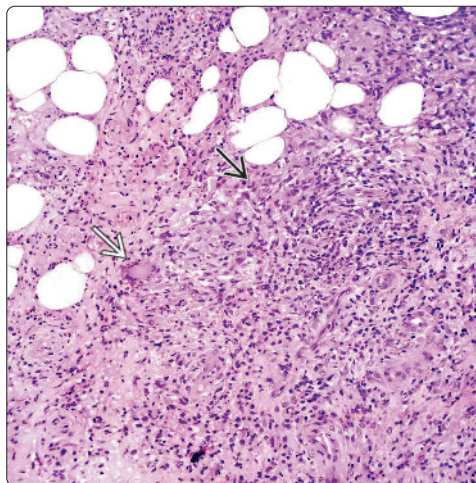


(Left) Erythema induratum of Bazin in this patient shows an ulcerated plaque on the posterior aspect of the leg. (Right) A biopsy of erythema induratum of Bazin demonstrates a lobular panniculitis [X] on low power.

**Vasculitis in Erythema Induratum of Bazin**



**Tuberculoid Granulomas in Erythema Induratum of Bazin**



(Left) High-power view of a biopsy of erythema induratum of Bazin demonstrates vasculitis [X] in a medium-sized vessel in the subcutaneous fat. (Right) Another high-power view of a biopsy of erythema induratum of Bazin demonstrates tuberculoid granulomatous formation [X] in the deep fat with multinucleated Langhans giant cells [X].



## Atypical Mycobacterial Infections

## KEY FACTS

## TERMINOLOGY

- Infections with *Mycobacterium* spp. other than *Mycobacterium leprae* and *Mycobacterium tuberculosis*

## CLINICAL ISSUES

- Tender nodules, abscesses, plaques, or ulcers
- May be solitary or multiple
- Erythema
- *Mycobacterium marinum* (swimming pool granuloma, fish tank granuloma)
  - May have history of swimming pool exposure or cleaning fish tank
- *Mycobacterium ulcerans* (Buruli ulcer, Bairnsdale ulcer)
  - Recent travel history to Africa
- *Mycobacterium avium-intracellulare*
  - History of immunosuppression, most commonly HIV/AIDS
- Treatment
  - In HIV patients, improve CD4 count through highly active antiretroviral therapy
  - In immunosuppressed patients, decrease immunosuppression
  - Antibiotics for *Mycobacterium* spp.

## MICROSCOPIC

- Hyperplastic epidermis ± ulceration
- Diffuse mixed infiltrate
- Granulomas ± caseation
- Mycobacterial organisms identified

## ANCILLARY TESTS

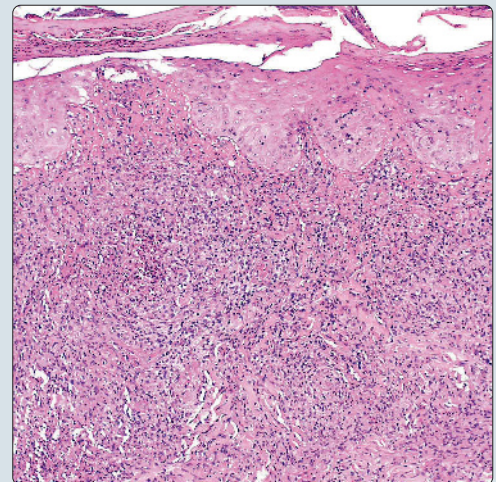
- Special stains: Acid-fast bacilli (AFB) or Fite stain
- PCR
- Culture
  - Most mycobacteria take several weeks to grow
  - *Mycobacterium fortuitum* and *Mycobacterium chelonae* grow in 1 week (rapid growers)

## Indurated Erythematous Nodule

(Left) Atypical mycobacterial infection over the dorsal hand presented as an indurated pink nodule ➡ in this patient. The culture was positive for *Mycobacterium marinum*. (Right) Some atypical mycobacterial infections have a diffuse mixed inflammatory infiltrate with associated necrosis. (Courtesy S. Billings, MD.)

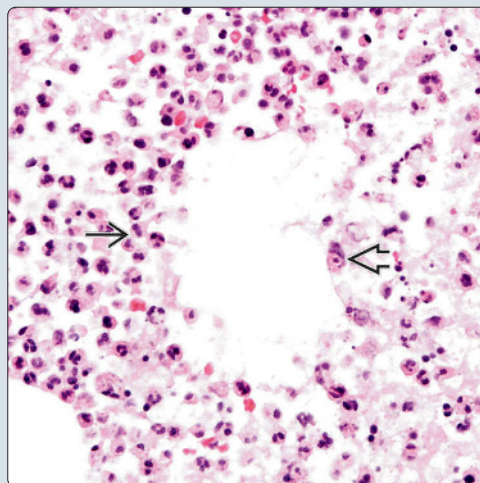


## Mixed Inflammatory Cell Infiltrate

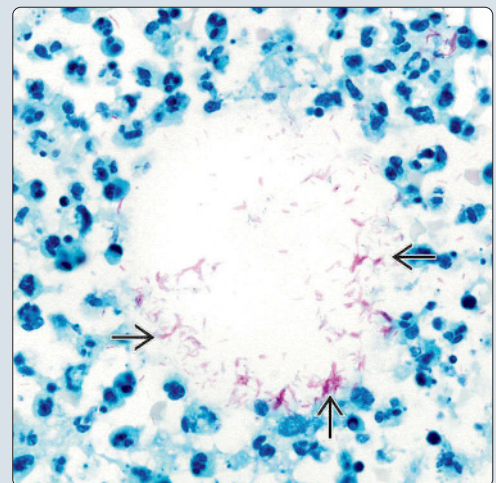


## Clear Spaces With Inflammation

(Left) In atypical mycobacterial infections, the mixed infiltrate may have clear spaces surrounded by neutrophils ➡ and histiocytes ➡. (Right) In these instances, an acid-fast bacilli stain will identify the bacteria ("red snappers") ➡ contained within the clear spaces. Cultures from this case grew *Mycobacterium chelonae*.



## Bacteria in Clear Spaces





## TERMINOLOGY

### Definitions

- Infections with *Mycobacterium* spp. other than *Mycobacterium leprae* and *Mycobacterium tuberculosis*

## CLINICAL ISSUES

### Epidemiology

- Age
  - Affects any age group
- Sex
  - No gender predilection
- Ethnicity
  - No specific ethnic predilection
    - More common in developing countries and immunosuppressed

### Site

- Can occur anywhere after bacterial contamination

### Presentation

- Tender nodules, abscesses, plaques, or ulcers
  - May be solitary or multiple
  - May be superficial, deep, or both
- Erythema

### Treatment

- Drugs
  - In HIV patients, improve CD4 count through highly active antiretroviral therapy
  - In immunosuppressed patients, decrease immunosuppression
  - Antibiotics for *Mycobacterium* spp.

### Prognosis

- Complete resolution with prompt treatment
- May have relapses or progression in immunosuppressed patients

### Clinical History

- *Mycobacterium marinum* (swimming pool granuloma, fish tank granuloma)
  - May have history of swimming pool exposure or cleaning fish tank
- *Mycobacterium ulcerans* (Buruli ulcer, Bairnsdale ulcer)
  - Endemic in some areas of Africa
  - Recent travel history to Africa
- *Mycobacterium avium-intracellulare*
  - History of immunosuppression, most commonly HIV/AIDS

## MICROSCOPIC

### Histologic Features

- General
  - Hyperplastic epidermis ± ulceration
  - Diffuse mixed infiltrate
    - Neutrophils, histiocytes, lymphocytes, plasma cells
    - May have granulomas ± caseation
- Specific
  - *M. marinum*
    - Poorly formed granulomas, typically no caseation

- May have prominent neutrophilic infiltration
- Can involve dermis or subcutis
- *M. ulcerans*
  - Extensive coagulative necrosis
  - May involve subcutaneous tissue as well
  - Secondary vasculitis may be present
- Other mycobacteria
  - Cause wide variety of lesions
  - High index of suspicion needed
  - *Mycobacterium fortuitum* and *Mycobacterium chelonae* are grown in culture within 1 week (rapid growers)

## ANCILLARY TESTS

### Histochemistry

- Acid-fast bacilli (AFB) or Fite stain
  - Positive in mycobacteria

### PCR

- Can be performed for speciation

### Microbiology Culture

- Most mycobacteria take several weeks to grow

## DIFFERENTIAL DIAGNOSIS

### Clinical and Histopathological

- Leprosy
  - Caused by *M. leprae*
  - AFB- and Fite-positive acid-fast organisms
  - May have well-formed granulomas or diffuse granulomatous inflammation
    - Accompanied by lymphocytic infiltrate
  - In United States, history of armadillo exposure is common
  - Erythematous rash with paresthesia
- Fungal infection
  - GMS- or PAS-positive fungal organisms
- Tuberculosis
  - Caused by *M. tuberculosis*
- Sarcoidosis
  - Tightly formed granulomas
    - Very little associated lymphocytic infiltrate
  - No caseation
  - No organisms or foreign bodies detected
- Foreign body
  - Typically well-formed granulomas
  - May have polarizable material within giant cells
- Tattoo granuloma
  - Granulomatous inflammation with tattoo pigment

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2. Suzuki K et al: Current status of leprosy: epidemiology, basic science and clinical perspectives. *J Dermatol.* 39(2):121-9, 2012
3. Cruz AT et al: Mycobacterial infections in Texas children: a 5-year case series. *Pediatr Infect Dis J.* 29(8):772-4, 2010
4. Lee WJ et al: Non-tuberculous mycobacterial infections of the skin: a retrospective study of 29 cases. *J Dermatol.* 37(11):965-72, 2010

# Leprosy

## KEY FACTS

### TERMINOLOGY

- Chronic infectious disease caused by bacteria *Mycobacterium leprae* and *Mycobacterium lepromatosis*

### CLINICAL ISSUES

- Bimodal distribution with peaks at 10-14 years and 35-44 years
- Leprosy is protean both clinically and histologically with various clinical presentations depending on host's immune system
- In affected patients, skin lesions, enlarged peripheral nerves, and skin anesthesia are 3 main signs of disease
- 8 different clinical presentations in patients susceptible to disease, each of which can be divided into pauci (low quantity) and multibacillary (high quantity), depending on bacterial load

### MICROSCOPIC

- Indeterminate leprosy:** Superficial and deep perivascular, periadnexal, and neurotropic lymphohistiocytic infiltrate

- Tuberculoid leprosy (TT):** Dermal granulomatous lymphohistiocytic infiltrate surrounding nerves
- Borderline tuberculoid (BT):** Periadnexal superficial and deep epithelioid granulomas with moderate lymphocytes and Langerhans-type giant cells
- Borderline lepromatous (BL):** Periadnexal granulomas composed of clumps of epithelioid cells and foamy macrophages with numerous lymphocytes surrounding all or portion of granuloma
- Lepromatous leprosy (LL):** Diffuse dermal infiltrate composed of foamy macrophages (lepra or Virchow cells) that spares papillary dermis (grenz zone)
- Histioid leprosy (HL):** Well-circumscribed lesion consisting of spindled and elongated histiocytes filled with numerous elongated bacilli

### ANCILLARY TESTS

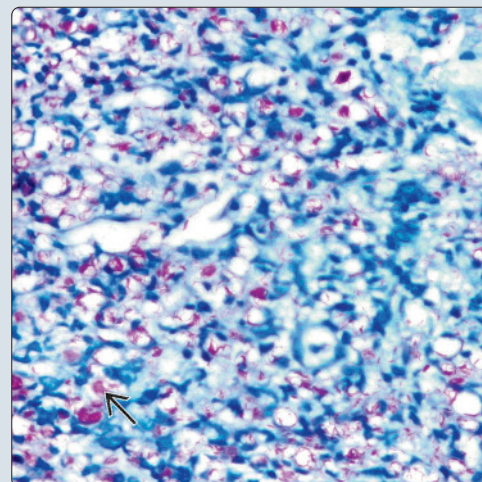
- Modified Ziehl-Neelsen (Fite-Faraco) stain is preferred: Stains bacilli bright red

### Leonine Facies

(Left) *Lepromatous leprosy (LL)* with diffuse infiltration of the face shows prominent superciliary arches giving rise to leonine facies. Madarosis and early saddle nose deformity is also present. (Courtesy S. Dogra, MD.) (Right) Fite stain of an oral lesion of LL demonstrates a striking, diffuse proliferation of positive, red-staining bacilli within foamy macrophages (Virchow cells). (Courtesy M. Ramos-e-Silva, MD, PhD.)

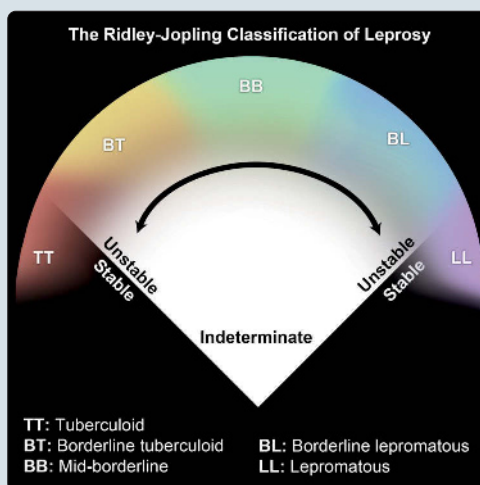


### Virchow Cells



### Ridley-Jopling Classification

(Left) Ridley-Jopling classification shows stable forms of disease at the tuberculoid (TT) and LL poles and immunologically unstable, borderline forms. The natural course of disease is "downward" from TT to LL forms. (Right) TT usually presents as a single, well-circumscribed, anesthetic lesion that is slightly hyperpigmented in light-skinned patients and hypopigmented in darker-skinned patients. (Courtesy S. Moschella, MD.)



### Solitary Anesthetic Plaque





## TERMINOLOGY

### Synonyms

- Hansen disease (HD)

### Definitions

- Chronic infectious disease caused by bacteria *Mycobacterium leprae* and *Mycobacterium lepromatosis*

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- *M. leprae* and *M. lepromatosis*
  - Acid-fast bacilli with slightly curved rod shape
  - Transmitted by nasal secretions after prolonged contact with untreated patients who have active disease
  - Humans are primary reservoir
    - However, leprosy can be transmitted to humans from 9-banded armadillos
- *M. lepromatosis* recently proposed as novel causative agent in diffuse lepromatous leprosy patients

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - 100-150 new cases reported in USA each year
    - Majority of cases are in California, Florida, Hawaii, Louisiana, Massachusetts, New York, and Texas
  - ~ 228,000 new cases reported worldwide each year
  - India, Brazil, and Indonesia have highest number of new reported cases
- Age
  - Bimodal distribution with peaks at 10-14 years and 35-44 years
- Sex
  - Lepromatous form more common in adult males
  - Tuberculoid form shows no gender predilection

### Presentation

- Leprosy is protean both clinically and histologically with various clinical presentations depending on host's immune system
- Most people (~ 95%) are not susceptible to infection
- In affected patients, skin lesions, enlarged peripheral nerves, and skin anesthesia are 3 main signs
  - Preferred affected sites are "cooler" areas of body
    - Acral skin, peripheral nerves, eyes, ears, nose, mucous membranes, testes
- WHO approach to clinical classification (paucibacillary or multibacillary) based upon number of lesions and number of bacilli present in skin smears from lesions
- Ridley-Jopling classification (proposed in 1966) categorizes leprosy into 5 major forms based on patient's immunologic response to infection
  - **Tuberculoid leprosy (TT):** Localized form consisting of 1 to a few well-circumscribed anesthetic hypopigmented lesions (in dark-skinned patients) or hyperpigmented lesions (in lighter skinned patients)
    - Lesions can be dry, scaly, and hairless; enlarged peripheral nerves may be seen nearby

- **Borderline leprosy (BC):** Includes **borderline tuberculoid (BT)**, **midborderline (BB)**, and **borderline lepromatous (BL)**
  - Although all forms of leprosy are associated with immunologic instability, this is most characteristic of borderline forms
  - **BT:** Lesions usually larger and more numerous than TT, usually 1 large lesion with surrounding satellite lesions
  - **BB (rare):** Several plaques, dome-shaped, or punched-out lesions with well-defined inner circle and poorly defined outer circle
  - **BL:** Similar to lepromatous leprosy but less severe, less mucosal involvement, and selective anesthesia of lesions
- **Lepromatous leprosy (LL):** Anergic form with symmetrical, widely distributed erythematous macules, papules, and nodules
  - Facial involvement can lead to deeply furrowed, lumpy face with prominent superciliary arches (leonine facies) and madarosis
  - Septal destruction or perforation can lead to saddle nose deformity
- Other clinical forms include
  - **Indeterminate leprosy (IL):** 1 to a few hypopigmented macules with minimal sensory loss
  - **Histioid leprosy (HL):** Rare form with firm cutaneous or subcutaneous erythematous, shiny papules, nodules, or plaques on normal skin
    - Often associated with relapse after therapy
- **Lepra reactions:** Emergency acute inflammatory reactions to *M. leprae* antigens commonly after treatment is started, during pregnancy, infection, or other inciting events in leprosy patients
- **Type 1 lepra reaction:** Can be upgrading/reversal or, more rarely, downgrading, and represents change in cellular immunity in leprosy patients
  - Typically affects borderline patients, but all types can be affected except IL
  - Natural course of leprosy is "down" toward lepromatous end of spectrum
  - Reversal of this normal trend is toward tuberculoid end of spectrum and closer to cure
  - **Upgrading/reversal:** Toward tuberculoid pole
    - Usually happens ≤ 6 months after therapy (acute); current lesions may enlarge and become erythematous and pruritic, but new lesions typically do not occur
  - **Downgrading:** Toward lepromatous pole
    - Happens ≥ 6 months after therapy; old skin lesions become swollen and painful, new lesions appear, and nerve damage is often progressive and extensive
    - Patients may have malaise, diffuse edema, and more extensive mucosal disease
    - Often occurs in inadequately treated patients
- **Type 2 lepra reaction:** a.k.a. erythema nodosum leprosum (ENL)
  - Hallmarks are painful, cutaneous red nodules or plaques
  - Occurs only in BL or LL after beginning treatment
- **Lucio phenomenon**

- Patients develop painful, pink, palpable skin nodules, typically on extremities, that are often ulcerated and can become infected, leading to sepsis and death
- Only seen in LL patients; primarily limited to Mexico and Central America

## Prognosis

- Most cases of IL resolve spontaneously
- Untreated leprosy can be very disfiguring
- Properly treated, leprosy now considered "curable"

## MICROSCOPIC

### Histologic Features

- Differs greatly depending on clinical form
- One useful clue to diagnosis is linearity of infiltrates, either following vessels or nerves
  - More obvious in TT, BT poles
- **IL:** Superficial and deep perivascular, periadnexal, and neurotropic lymphohistiocytic infiltrate
  - Bacilli usually not present but may be seen in small numbers near small nerves
- **TT:** Superficial and deep periadnexal epithelioid granulomas with numerous lymphocytes and occasional Langerhans-type giant cells
  - Involvement of epidermis by granulomas or more often lymphocytes in 1/2 of cases
    - Exocytosis of lymphocytes common
  - Perivascular lymphocytic infiltrate in nearly all cases
  - Bacilli usually difficult to find, even with stains
- **BT:** Periadnexal superficial and deep epithelioid granulomas with moderate lymphocytes and Langerhans-type giant cells
  - Perivascular lymphocytic infiltrate in almost all cases
  - Perineural lymphocytic infiltrate with grenz zone in most cases
  - Bacilli still difficult to identify but can often be found in small numbers with special stains
- **BL:** Periadnexal granulomas composed of clumps of epithelioid cells and foamy macrophages with numerous lymphocytes surrounding all or portion of granuloma
  - Grenz zone in almost all cases
  - Bacilli usually easy to identify and much more numerous than in other borderline forms
  - Sometimes in BL and LL, clumps of bacilli (globi) can be visualized within cells on H&E alone
- **LL:** Diffuse dermal infiltrate composed of foamy macrophages (lepra or Virchow cells) often infiltrating between nerve fibers
  - Grenz zone in nearly all cases
  - Striking proliferation of bacilli seen within cytoplasm of Virchow cells with special stains
- **HL**
  - Well-circumscribed lesion consisting of spindled and elongated histiocytes with slightly vacuolated cytoplasm forming linear bands and whorls
    - Histiocytes contain numerous cytoplasmic (often elongated) bacilli, but histiocytes are typically not as vacuolated as classic Virchow cells in LL
- **Type 1 upgrading/reversal** reaction
  - Edema, increased lymphocytes, giant cell formation, and formation of groups of epithelioid cells

- **Type 1 downgrading** reaction
  - Decreased lymphocytes and epithelioid cells with replacement by macrophages, fibrosis, and more numerous bacteria
  - Comparison of previous biopsy specimen helpful when determining whether reaction is type 1 upgraded or type 1 downgraded
- **Type 2** lepra reaction or ENL
  - Papillary dermal edema, intense inflammatory infiltrate composed of lymphocytes, neutrophils, and Virchow cells that extend into surrounding subcutaneous fat
- **Lucio phenomenon:** 2 patterns seen
  - Thrombotic vasculopathy with skin ulceration, mild mononuclear infiltrate, and necrosis; necrosis can affect entire dermis, subcutaneous tissue, and underlying fascia
  - Leukocytoclastic vasculitis-like pattern

## ANCILLARY TESTS

### PCR

- Only works when acid-fast bacilli are visible on staining; not useful for formalin-fixed tissue

### Special Stains

- Modified Ziehl-Neelsen (Fite-Faraco) stain is preferred
  - Viable organisms stain bright red
  - Dead or degenerated bacilli stain irregularly or negatively
- Gomori methenamine silver
  - Can identify acid-fast-negative debris of organisms

## DIFFERENTIAL DIAGNOSIS

### Histologic (Mimics of TT, LL, HL)

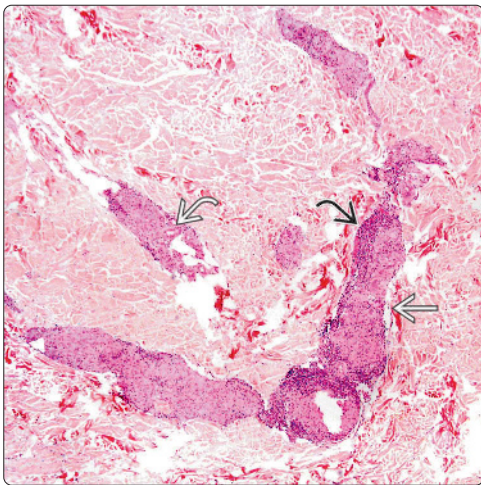
- Tuberculoid leprosy (TT)
  - Tuberculosis, atypical mycobacterial infections, histoplasmosis, cat scratch disease, syphilis, and other infectious granulomatous diseases can mimic TT
  - Sarcoid, foreign body reactions, and other noninfectious granulomatous diseases can mimic TT
  - Neurotropic granulomatous and lymphohistiocytic infiltrate should point toward TT and at least mandate mention in histologic differential
  - Clinicopathologic correlation necessary (special stains typically unhelpful due to low numbers of bacteria)
- LL
  - Xanthoma, rhinoscleroma, malakoplakia, leishmaniasis, atypical mycobacterial infections, histiocytic proliferations, others
  - Grenz zone and enlarged, almost atypical-looking histiocytes (Virchow cells) would favor LL
  - Special stains and clinicopathologic correlation helpful
- HL
  - Dermatofibroma (DF) is main differential
    - Grenz zone and dermal proliferation of spindled histiocytes are common to both HL and DF
  - Recognition of organisms ± use of special stains is diagnostic of HL

## SELECTED REFERENCES

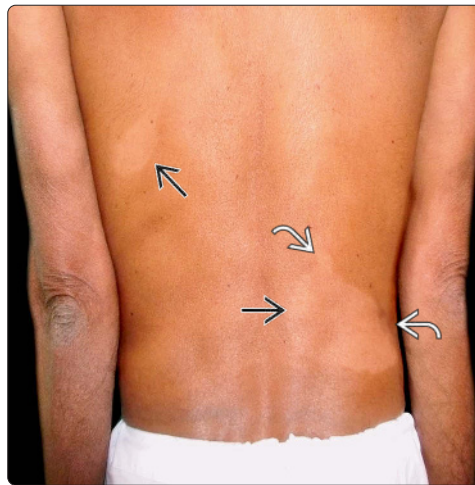
1. Rongioletti F et al: Leprosy: a diagnostic trap for dermatopathologists in nonendemic area. *Am J Dermatopathol*. 31(6):607-10, 2009



**Granulomas Along Nerves**

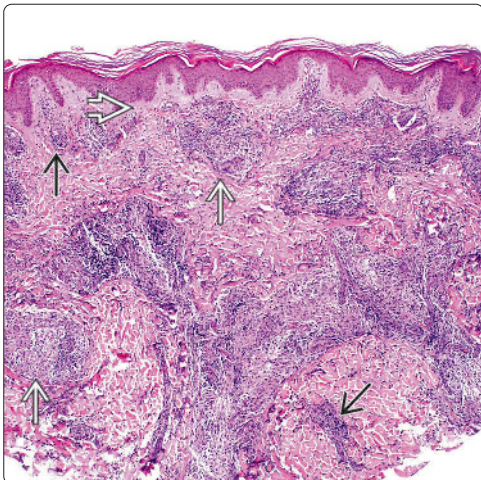


**Hypopigmented Patches**

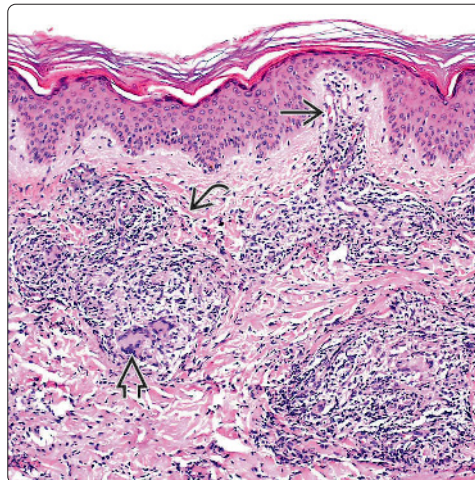


(Left) Biopsy from a patient with TT leprosy demonstrates deep, linear, epithelioid granulomas surrounding neurovascular bundles, also with numerous lymphocytes. Even with the use of special stains, bacilli are often not seen. (Right) Borderline tuberculoid presents similarly to TT. However, anesthetic hypopigmented lesions (as seen in this dark-skinned patient) are often larger, more ill-defined, and greater in number, with small surrounding satellite lesions. (Courtesy S. Dogra, MD.)

**Grenz Zone**

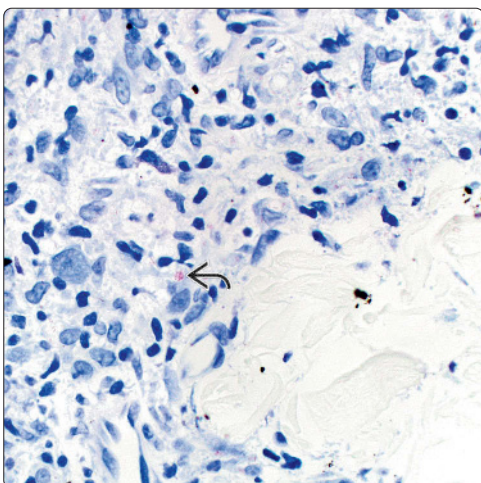


**Langerhans-Type Giant Cells**



(Left) BT demonstrates superficial and deep epithelioid cell granulomas, a moderate superficial and deep perivascular lymphocytic infiltrate, and a positive grenz zone. (Right) High-power view of BT leprosy demonstrates a grenz zone, a superficial lymphocytic perivascular infiltrate, and superficial epithelioid granulomas with Langerhans-type giant cells. (Courtesy S. Billings, MD.)

**AFB**



**BB Leprosy**



(Left) Fite stain of BT lesion shows a few rare acid-fast bacilli (AFB) within a foamy macrophage. In TT, it is usually very difficult to demonstrate bacilli even with special stains. BT lesions typically show rare to occasional bacilli, and borderline leprosy (BL) and LL lesions typically demonstrate numerous easily identifiable bacilli with special stains. (Right) Patient with midborderline (BB) leprosy shows a typical punched-out lesion with a well-defined inner border & ill-defined outer border. These features are classic for BB leprosy clinically.



BL Leprosy

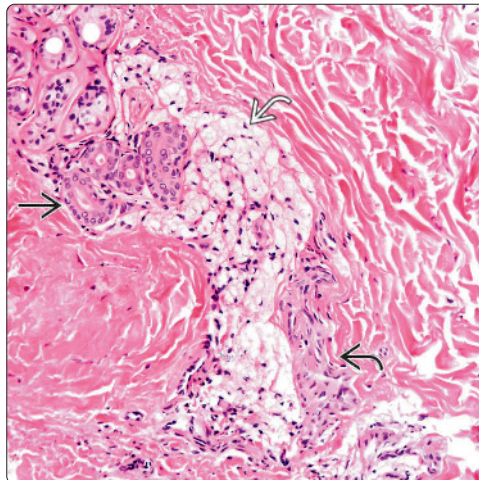


BL Leprosy

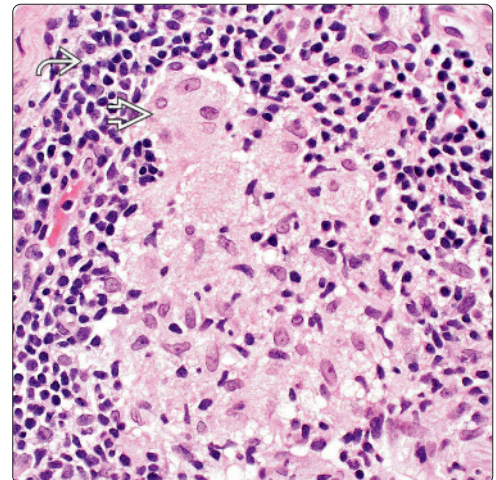


(Left) BL leprosy presents as multiple, symmetrical, infiltrative, hypopigmented macules spread across the trunk. Coalescence in some areas indicates disease downgrading toward LL. (Courtesy S. Dogra, MD.) (Right) An example of BL leprosy demonstrates an erythematous nodule directly in front of the ear, indicating involvement of the preauricular nerve.

Virchow Cells

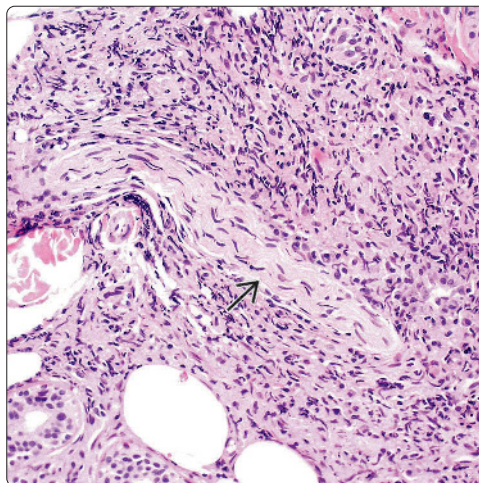


Foamy Macrophages

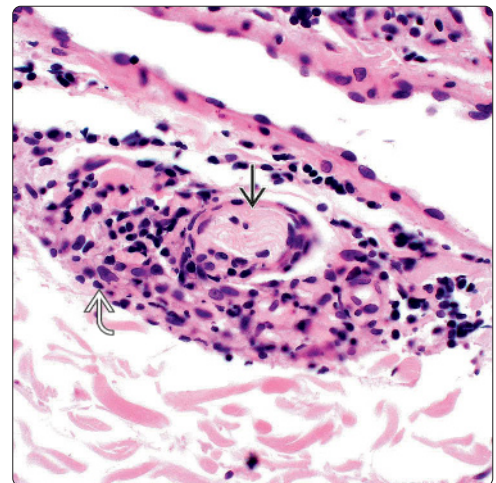


(Left) Biopsy of BL leprosy demonstrates granulomas of vacuolated macrophages or Virchow cells surrounding adnexal structures and even a nerve in the deep dermis. (Right) High-power view from a biopsy of BL leprosy demonstrates granulomas composed of foamy macrophages with numerous lymphocytes surrounding the granuloma. (Courtesy S. Billings, MD.)

Granulomas Tracking Nerve



Lymphocytic Infiltrate Involving Nerve



(Left) High-power view of a case of BL leprosy demonstrates a nerve surrounded by an epithelioid granuloma and numerous lymphocytes. (Courtesy S. Billings, MD.) (Right) High-power view of BL leprosy demonstrates a lymphohistiocytic inflammatory infiltrate surrounding and destroying a nerve. (Courtesy S. Billings, MD.)



**Lepromatous Leprosy**

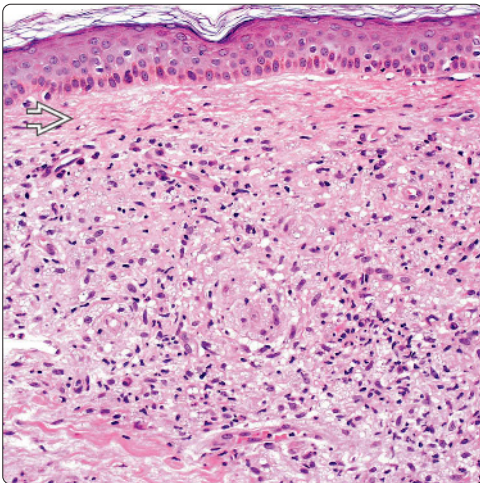


**Lepromatous Leprosy Involving Helix**

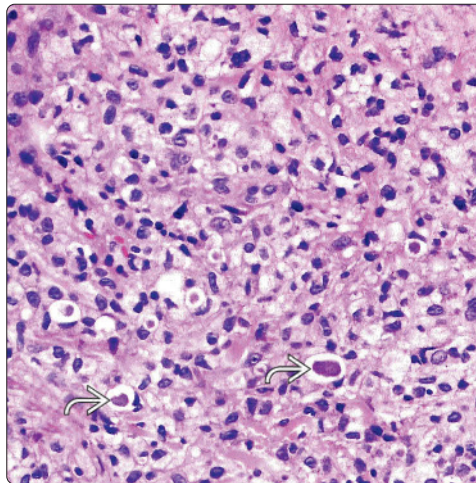


(Left) LL demonstrates diffuse infiltration with nodules involving the ear lobules and LL nodules involving the face. (Courtesy S. Dogra, MD.) (Right) Clinical photo of LL shows nodules causing deformities of the aural helix. LL is symmetric, bilateral, and often affects other organs. Leprosy prefers cooler areas of the body, such as the ears, nose, and peripheral nerves. (Courtesy M. Ramos-e-Silva, MD, PhD.)

**Grenz Zone**

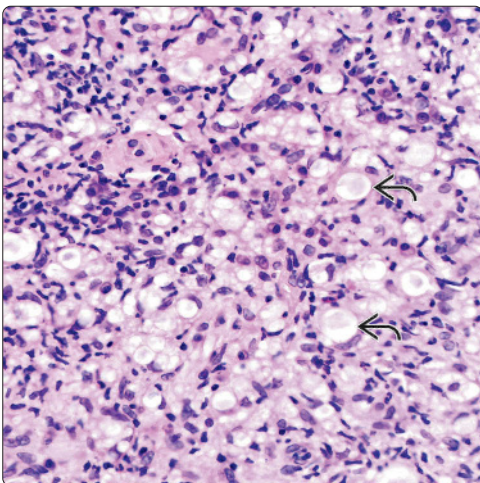


**Globi**

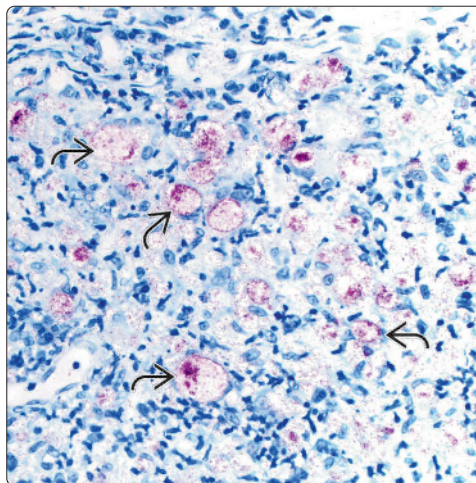


(Left) LL demonstrates a grenz zone in almost all cases, and also shows a diffuse infiltrate of foamy macrophages (also called lepra or Virchow cells) that are often filled with bacilli, which are easily seen with special stains. (Courtesy S. Billings, MD.) (Right) In BL or LL, occasionally clumps of bacilli called globi can be appreciated on H&E sections alone.

**Lepra Cells**



**Fite Stain of LL**



(Left) A case of LL demonstrates numerous foamy macrophages (Virchow or lepra cells) typically throughout the dermis with numerous AFB evident on special stains. (Right) Fite stain from a biopsy of a patient with LL demonstrates innumerable AFB within foamy macrophages or Virchow cells.



**Type 1 Reaction**

(Left) In type 1 reactions, previous lesions become more erythematous and infiltrated. This patient with BT had a "downgrading" type 1 reaction. SLE and drug reactions are common clinical differentials. (Courtesy S. Dogra, MD.) (Right) Histologic correlation is crucial in leprosy because of the protean clinical manifestations of leprosy. A severe type 1 "downgrading" reaction in this patient with BT clinically mimicked a severe cellulitis. (Courtesy S. Dogra, MD.)

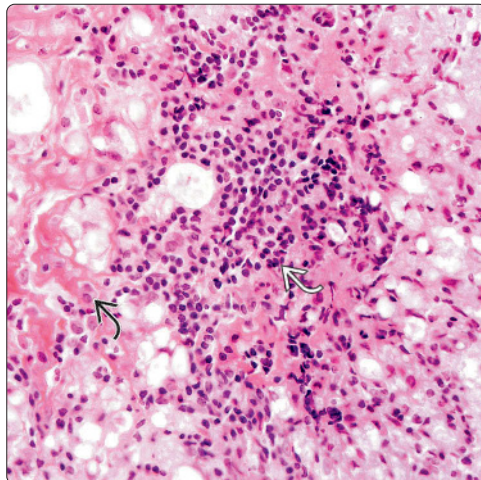


**Severe Type 1 Reaction**



**Type 1 Upgrading (Reversal)**

(Left) Histology of a type 1 upgrading or "reversal" reaction demonstrates increased lymphocytes and the formation of groups of epithelioid cells. (Right) A type 2 reaction or erythema nodosum leprosum (ENL) presents as painful, cutaneous red nodules or plaques.

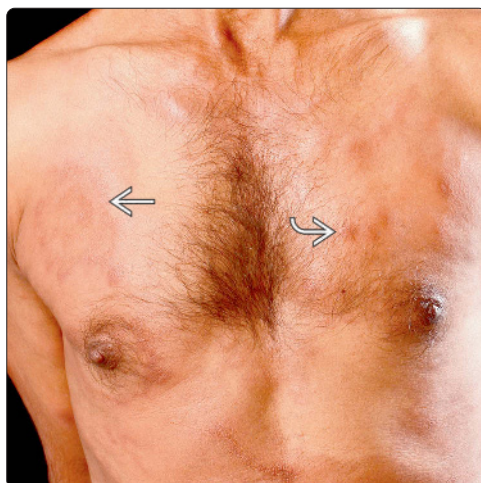


**Type 2 Reaction**

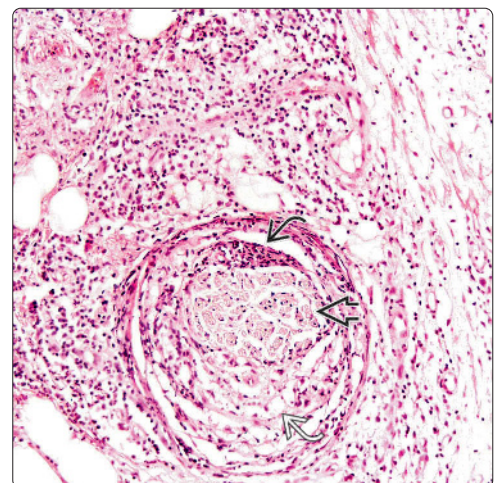


**Erythema Nodosum Leprosum**

(Left) An example of ENL demonstrates numerous, tender, red nodules and plaques of varying size in this patient. (Courtesy S. Dogra, MD.) (Right) Type 2 lepra reactions histologically demonstrate an intense inflammatory infiltrate composed of lymphocytes, neutrophils, and Virchow cells that extend into surrounding subcutaneous fat and surround the nerves.

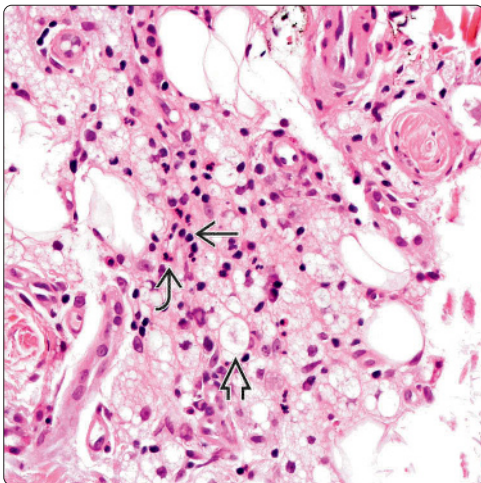


**Type 2 Lepra Reaction**





Type 2 Reaction



Lucio Phenomenon

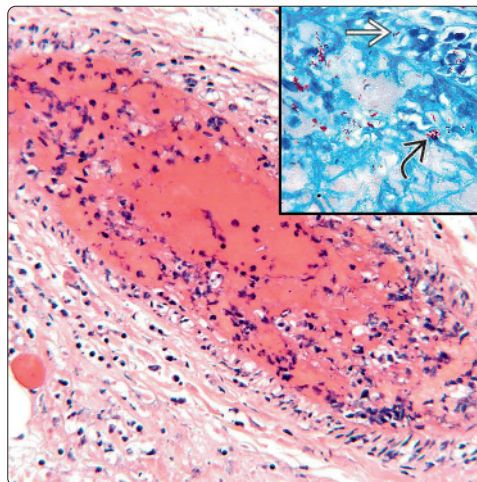


(Left) High-power view of biopsy from a type 2 reaction demonstrates an intense inflammatory infiltrate composed of lymphocytes [box], neutrophils [box], and Virchow cells [box] that extend into surrounding subcutaneous fat. (Right) Lucio phenomenon occurs in LL patients mainly in Mexico and Central America. It is characterized by painful skin nodules on the extremities that often ulcerate and become infected, leading to sepsis and even death. (Courtesy S. Moschella, MD.)

Lucio Phenomenon

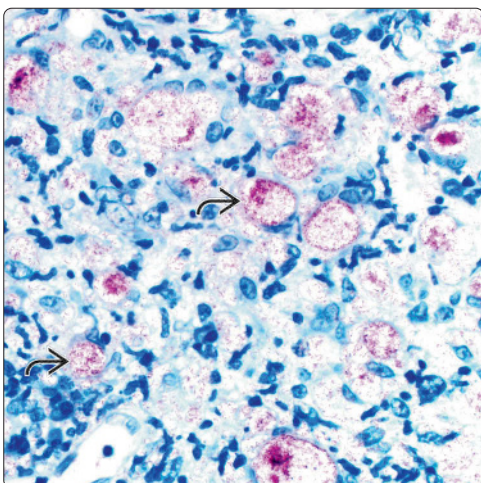


Thrombus With AFB

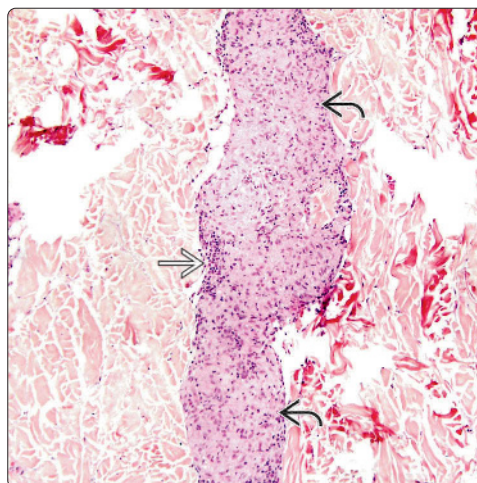


(Left) Another case of Lucio phenomenon shows ulcerated skin nodules. (Courtesy E. Kraus, MD.) (Right) This biopsy of Lucio phenomenon shows a thrombotic vasculopathy pattern with a large thrombus in a vessel, surrounding mononuclear inflammation, and a mild endothelial proliferation that can be quite marked at times. A Fite stain of this biopsy demonstrates positive staining AFB within the thrombus [box] and vessel wall [box]. (Courtesy D. Scollard MD, PhD.)

AFB in Fite Stain



TT Leprosy



(Left) High-power view of a Fite stain demonstrates numerous AFB within lepra cells [box]. Borderline lesions typically demonstrate much fewer AFB in tissue biopsies, while TT lesions typically will not show demonstrable AFB, even with special stains. (Right) Higher power of a biopsy of TT leprosy demonstrates a large dermal granuloma composed of numerous epithelioid histiocytes [box] and collections of lymphocytes [box]. Bacilli even with use of special stains are often not seen.



## Cat Scratch Disease/Bacillary Angiomatosis

## KEY FACTS

## ETIOLOGY/PATHOGENESIS

- Domestic cats represent natural reservoir and vectors
- Cat scratch disease (CSD) is caused by *Bartonella henselae*, and bacillary angiomatosis (BA) is caused by both *B. henselae* and *Bartonella quintana*

## CLINICAL ISSUES

- History of recent exposure to cats (scratch, bite, lick)
- Papules or pustules appear at inoculation site in 3-12 days
- Regional lymphadenopathy usually occurs after 10-30 days
- Immunocompromised patients develop BA
- Usually mild constitutional symptoms, including malaise, anorexia, nausea, fatigue, headache, and low-grade fever

## MICROSCOPIC

- Cutaneous lesions of CSD show zone of necrosis, fibrin, neutrophils, and nuclear debris in dermis surrounded by mantle of macrophages, lymphocytes, and plasma cells

- Cutaneous lesions of BA are characterized by vascular proliferation in lobular pattern
- Accompanied by lymphocytes, histiocytes, neutrophils, and nuclear dust of neutrophils and clumps of granular purplish material (masses of bacteria) in immediate vicinity of some vessels

## ANCILLARY TESTS

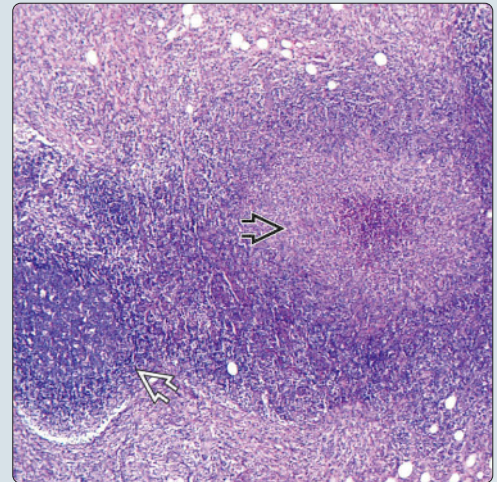
- Immunohistochemistry
  - Monoclonal antibody against *B. henselae* has no cross-reactivity with other *Bartonella* strains
- Special stain
  - Warthin-Starry stain
- PCR
  - Very useful with nonspecific histopathology or cases with negative serology
- Serology
  - Most practical; best performed 6-8 weeks after onset
  - Titers > 1:250 strongly suggest active or recent infection

## Ulcerated Papule With Lymphadenopathy

(Left) This is an ulcerated papule at the site of inoculation with regional submandibular lymphadenopathy in a case of cat scratch disease (CSD). (Right) H&E demonstrates the microscopic features of CSD lymphadenitis, showing hyperplastic follicles and stellate necrotizing granulomas.

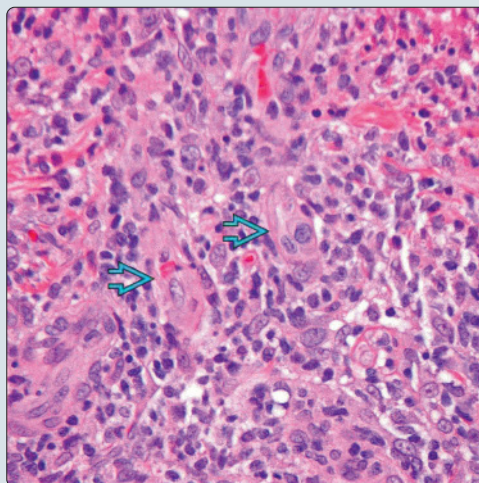


## Necrotizing Granulomas in Lymph Node

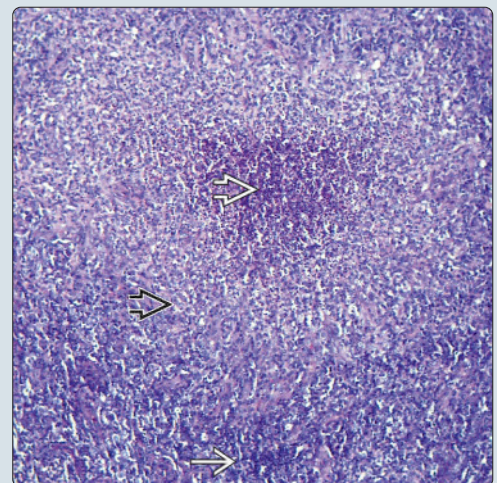


## Blood Vessels and Lymphocytes

(Left) High-power field reveals a proliferation of small blood vessels and a mixed inflammatory cell infiltrate adjacent to the zone of necrosis. (Right) High-power field of the necrotizing granuloma shows central zone of necrosis, cellular debris, clusters of neutrophils surrounded by palisading histiocytes, and an outer zone of lymphocytes and plasma cells.



## Neutrophils and Necrosis





## TERMINOLOGY

### Abbreviations

- Cat scratch disease (CSD)
- Bacillary angiomatosis (BA)

### Synonyms

- CSD
  - Cat scratch fever
  - Benign inoculation lymphoreticulosis
  - Regional granulomatous lymphadenitis
- BA
  - Epithelioid angiomatosis

### Definitions

- CSD: Self-limiting infectious disease characterized by subacute, regional lymphadenitis, usually following scratch or bite of cat
- BA: Infectious disease that appears in immunocompromised persons, usually with HIV/AIDS, following scratch or bite of cat, characterized by vasoproliferative lesions usually, but not exclusively, seen in skin

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- Natural reservoir and vectors are domestic cats, especially kittens and stray cats
- Occasional cases of CSD associated with dog and monkey bites reported

### Infectious Agents

- *Bartonella henselae* (formerly *Rochalimaea henselae*)
  - Causative agent of CSD, BA, and endocarditis
  - Small, pleomorphic, intracellular, slow-growing, weakly gram-negative bacillus
  - Houston-1 and Marseille (genotype II) identified as main genogroups
- *Bartonella quintana*
  - Causative agent of both trench fever and BA
  - Less frequently associated with BA than *B. henselae*
- *Bartonella clarridgeiae* rarely associated with CSD cases

### Pathogenesis

- Only genus that infects human erythrocytes and triggers pathological angiogenesis in vascular bed
- Highly adapted pathogens that infect and persist in erythrocytes and endothelial cells of host circulatory system through various mechanisms
  - Induction of pathological angiogenesis, with concomitant production of pseudoneoplastic lesions in human vasculature (i.e., BA and bacillary peliosis)
  - Use of adhesins for endothelial cells
  - Incorporation of lipopolysaccharides with low endotoxic potency in outer membrane (antagonistic to host's innate immune response)
- Colonization of secondary foci at considerable distances from primary site of infection, with preference for highly vascularized tissues like heart valves, liver and spleen, or cooler areas of body, such as vascular beds of skin
- Response to infection depending on immune status of infected host

- Granulomatous and suppurative response in immunocompetent individuals
- Vasoproliferative response in immunocompromised persons

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - At least 9.3 per 100,000 population for CSD
  - Greater in regions with higher temperature and humidity
  - Incidence peaks in fall and winter months
- Age
  - CSD affects persons in all age groups, but most are younger than 21 years (60-80%)
- Sex
  - CSD and BA more common in males
- Ethnicity
  - CSD more common in whites

### Presentation

- History of recent exposure to cats (scratch, bite, lick)
- 1 or more cutaneous papules or pustules may appear at inoculation site in 3-12 days
- Regional lymphadenopathy (most remarkable manifestation) usually occurs after 10-30 days
  - Cervical, axillary, or epitrochlear nodes typically involved
- Usually mild constitutional symptoms, including malaise, anorexia, nausea, fatigue, headache, and low-grade fever
- Atypical presentation in up to 10% of cases
  - Encephalopathy, neuroretinitis, prolonged fever, arthritis, synovitis, atypical pneumonitis, and endocarditis
  - Granulomatous conjunctivitis and ipsilateral preauricular lymphadenitis (Parinaud oculoglandular syndrome) caused by conjunctival inoculation
- Visceral involvement with hepatitis/splenitis
- Skin manifestation, including nonspecific rashes, erythema nodosum, and leukocytoclastic vasculitis
- Immunocompromised patients may develop BA, bacillary peliosis, or persistent or relapsing fever with bacteremia
  - BA
    - Vasculoproliferative disease that primarily involves skin but can involve other organs
    - Numerous brown to violaceous tumors of skin and subcutaneous tissues
    - Lesions very similar to verruga peruana, the chronic form of Carrión disease (Oroya fever)

### Laboratory Tests

- Diagnosis of both CSD and BA strongly suggested by history and physical findings
- Laboratory findings
  - Occasionally mildly elevated white blood cell count, elevated or diminished platelet count, and elevated erythrocyte sedimentation rate in CSD
  - Anemia, leukopenia, CD4(+) cell count < 200/ $\mu$ L in patients with BA and HIV

### Treatment

- Options, risks, complications
  - Most cases of CSD require only supportive and symptomatic care

# Cat Scratch Disease/Bacillary Angiomatosis

- Management of mild-to-moderate infections in immunocompetent patients consists of reassurance, adequate follow-up, and analgesics for pain
- Antibiotic treatment (azithromycin, erythromycin, doxycycline, or gentamicin) is necessary for severe infections, particularly when lymph nodes are severely affected and when organs other than lymph nodes have become involved
- Immunocompromised patients tend to develop more severe *Bartonella* infections and may require prolonged antibiotic treatment
- Avoidance of unnecessary manipulation, including incision and drainage of lymph nodes, is advisable as this may leave scars without hastening recovery
- Surgical approaches
  - Occasionally, lymph node aspiration is indicated for symptomatic relief of tender, fluctuant nodes
  - Excision of lymph nodes is not justified therapeutically, although it may occasionally be indicated for histology

## Prognosis

- Infections usually resolve without sequelae in 1-6 months in 90% of immunocompetent patients
- Immunocompromised patients may develop severe, disseminated disease
- Overall prognosis depends on early detection, treatment, and degree of immunosuppression

## IMAGING

### General Features

- Pulmonary parenchymal nodules revealed by chest radiography in BA
- Hypoechoic lesions in spleen, liver, and lymph nodes on ultrasonography
- Characteristic hypodense ring-like lesions on CT scan in peliosis hepatis
- Multiple diffuse low- or high-attenuation lesions scattered throughout hepatic parenchyma on contrast-enhanced CT in BA

## MICROSCOPIC

### Histologic Features of Cutaneous CSD Lesions

- Zone of necrosis, fibrin, neutrophils, and nuclear debris in dermis surrounded by mantle of macrophages, lymphocytes, and plasma cells
- Round, triangular, or stellate granulomas often with numerous neutrophils in center
- Overlying pseudoepitheliomatous hyperplasia
- Organisms present within macrophages and lying free, particularly in areas of necrosis and suppuration

### Histologic Features of Cutaneous BA Lesions

- Spectrum of histologic findings
  - Superficial pyogenic granuloma (PG)-like paucibacillary lesions
  - Deep, densely cellular multibacillary lesions with abundant neutrophils and leukocytoclasia
  - Pseudomalignant variants with numerous atypical endothelial cells and mitoses
  - Fibrotic end-stage lesions with abundant siderophages

- Lobular pattern with prominent proliferation of small round blood vessels in edematous stroma, separated by connective tissue septa but less evident than in PG
- Blood vessels lined by plump endothelial cells that protrude into vascular lumens
- Lymphocytes, histiocytes, neutrophils, and nuclear dust of neutrophils scattered throughout lesion
- Clumps of granular purplish material (masses of bacteria) of variable size positioned in immediate vicinity of some vessels, accompanied by neutrophils

## ANCILLARY TESTS

### Immunohistochemistry

- Monoclonal antibody against *B. henselae* commercially available with no cross-reactivity with other *Bartonella* strains

### PCR

- Very useful in confirming clinically suspected lesions with nonspecific histopathology or cases with negative serology
- Minimally invasive and highly accurate procedure that can be done on tissue or blood, fresh or frozen specimens
- Most sensitive test that differentiates between different *Bartonella* species, as well as between subspecies and strains
- High specificity and rapid identification

### Serologic Testing

- Most practical diagnostic tool; best performed 6-8 weeks after onset of disease
- Variable sensitivity [IFA 96% and enzyme-linked immunosorbent assay (ELISA) 71%]
- Titers > 1:250 strongly suggest active or recent infection
- Positive laboratory serology findings can confirm diagnosis, but negative result does not rule out disease
- Novel IgM-specific ELISA test for diagnosis of acute infections with *B. henselae* has recently been developed
  - 100% sensitivity and 97.1% specificity

### Electron Microscopy

- Bacilli identified as pleomorphic structures with trilaminar wall and electron-dense granular cytoplasm

### Histochemistry

- Organisms demonstrated by Warthin-Starry stain or Brown-Hopps modification of Gram stain
  - Clumps of black bacilli positioned both interstitially and near blood vessels in cutaneous lesions of BA
  - Appear as black bacilli within macrophages and lying free, particularly in areas of necrosis and suppuration in cutaneous lesions of CSD
  - Singly, in chains, or in large clumps in macrophages in necrotic areas, in sinus histiocytes, or in extracellular space in lymph node lesions of CSD
    - Most numerous in early stages within monocytoïd B cells
    - Difficult to detect in well-developed stellate abscesses

### Intradermal Skin Test

- No longer widely available because of concern for potential transmission of hepatitis viruses, HIV, and prions



**Microbiology**

- Bacterial cultures from blood and tissues
  - Slow-growing and difficult to isolate bacteria

**DIFFERENTIAL DIAGNOSIS****Differential Diagnosis of CSD**

- Hidradenitis suppurativa
  - Painful erythematous papules, nodules, tender abscesses, and sometimes draining sinus tracts with predilection for intertriginous regions
  - Suppurative granulomatous inflammation in dermis with formation of sinuses lined by stratified squamous epithelium
  - Pseudoepitheliomatous hyperplasia
- Deep fungal infections
  - Keratotic, crusted, and ulcerated lesions
  - Suppurative granulomatous inflammation with pseudoepitheliomatous hyperplasia
  - Organisms identified in tissue sections by special stains (PAS, silver-methenamine, mucicarmine), by growth in culture, or by PCR
- Atypical mycobacterial infections
  - Verrucous, keratotic, or crusted papules, plaques, nodules, abscesses, or ulcers
  - Suppurative granulomatous dermatitis with pseudoepitheliomatous hyperplasia
  - Acid-fast bacilli identified by Ziehl-Neelsen stain, culture on Lowenstein-Jensen media, or by PCR
- Lymphogranuloma venereum
  - Papule, ulcer, or herpetiform vesicle usually on genitals followed by regional lymphadenopathy
  - Histologically similar to CSD
  - Etiologic agent *Chlamydia trachomatis* stains black with Warthin-Starry stain techniques and gram negative with Brown-Hopps stain
  - Distinction from CSD relies on serological testing
- Tularemia
  - Papules at site of inoculation followed by regional lymphadenitis
  - Suppurative granulomatous inflammation similar to CSD
  - Etiologic agent represented by *Francisella tularensis*, gram-negative coccobacillary bacteria
  - Diagnostic confirmation by serology, culture, or PCR
- Other differential diagnoses to be considered
  - Other infections (syphilis, brucellosis, toxoplasmosis, infectious mononucleosis, leishmaniasis)
  - Kikuchi disease
  - Nodal lymphomas

**Differential Diagnosis of BA**

- Verruga peruana
  - Indistinguishable clinically and histopathologically from BA
  - Occurs in immunocompromised patients
  - Characterized by proliferation of capillaries and venules
  - Exhibits inflammatory infiltrate with more lymphocytes and plasma cells (vs. mainly neutrophils in BA)
  - Infectious agent represented by *Bartonella bacilliformis* forming intracellular inclusions termed Rocha-Lima bodies

- PG
  - Usually solitary lesion, no associated immune deficiency
  - Lobulated proliferation of small vessels in edematous stroma with fibrous septa
  - Muscle-containing blood vessel feeder
  - Absence of nuclear dust of neutrophils
  - No clumps of purplish granular material
- Kaposi sarcoma
  - Macules, patches, papules, and plaques
  - Spindle-cell proliferation with slit-like spaces containing erythrocytes, accompanied by lymphoplasmacytic infiltrate, extravasated erythrocytes, and siderophages
  - Hyaline globules within some endothelial cells
  - Invariably associated with human herpesvirus 8
- Epithelioid hemangioma/angiolymphoid hyperplasia with eosinophilia
  - Angiomatoid papules or nodules predominantly located on head, especially around ears
  - Irregular thick-walled blood vessels lined by plump endothelial cells that protrude into lumen
  - Endothelial cells with large round to oval nuclei, abundant eosinophilic cytoplasm, and prominent vacuoles
  - Dense inflammatory infiltrate with lymphocytes, numerous eosinophils, and histiocytes

**DIAGNOSTIC CHECKLIST****Clinically Relevant Pathologic Features**

- Report contact with cats, especially kittens

**Pathologic Interpretation Pearls**

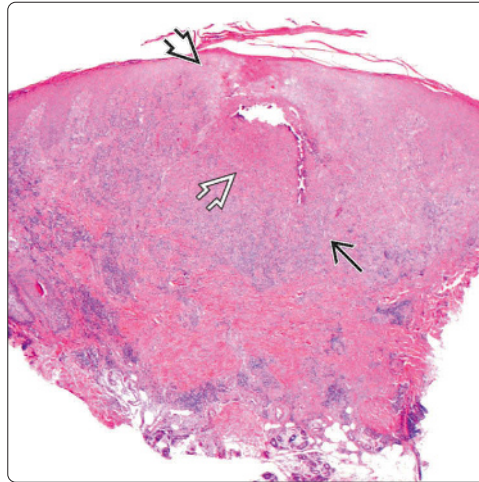
- Suppurative granulomatous dermatitis with extensive necrosis and stellate abscesses are clues to CSD
- Neutrophils and nuclear "dust" of neutrophils and clumps of purplish granular material in vicinity of venules in PG-like lesion are clues to BA

**SELECTED REFERENCES**

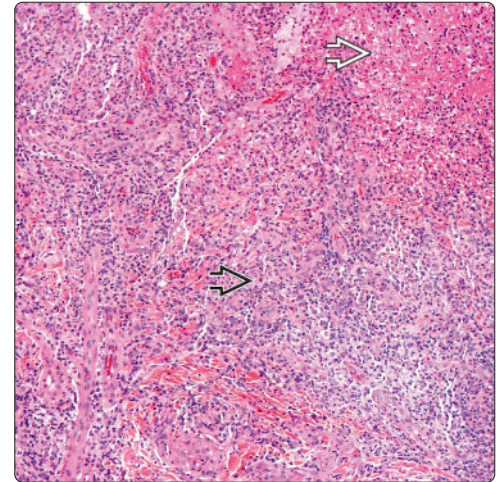
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(Left) Central zone of suppuration surrounded by abundant inflammatory infiltrate and pseudoepitheliomatous hyperplasia of the superjacent epidermis are highly indicative of an infectious process, as in this case of CSD. (Right) This is a close-up view of the zone of suppuration with extensive necrosis surrounded by a mixed inflammatory cell infiltrate composed of lymphocytes, histiocytes, neutrophils, and plasma cells.

Suppuration With Epidermal Hyperplasia

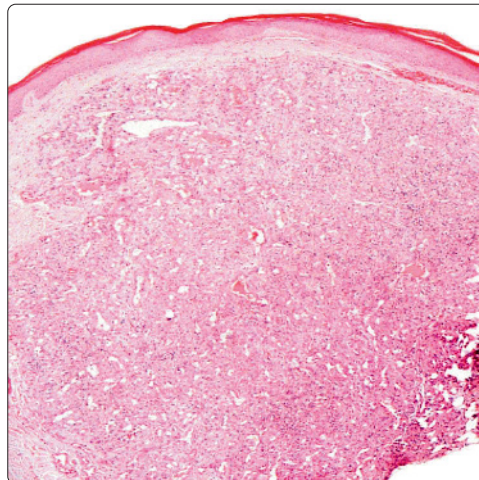


Necrosis and Acute Inflammation

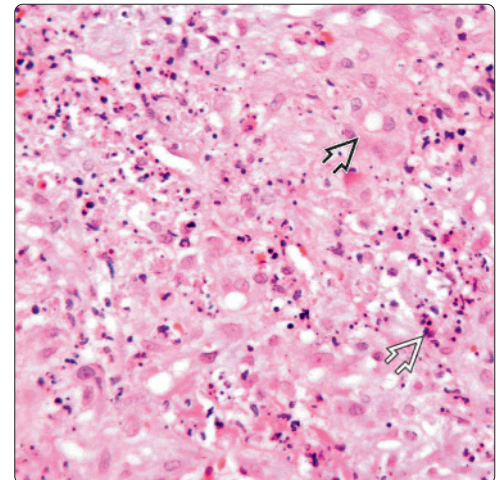


(Left) This is a dome-shaped nodule of bacillary angiomatosis (BA) consisting of a dense, small vessel proliferation with intermixed inflammation. (Right) Here is a proliferation of small vessels lined by plump endothelial cells, abundant neutrophils, and nuclear dust of neutrophils in a pyogenic granuloma (PG)-like lesion that is highly indicative of BA.

Blood Vessel Proliferation

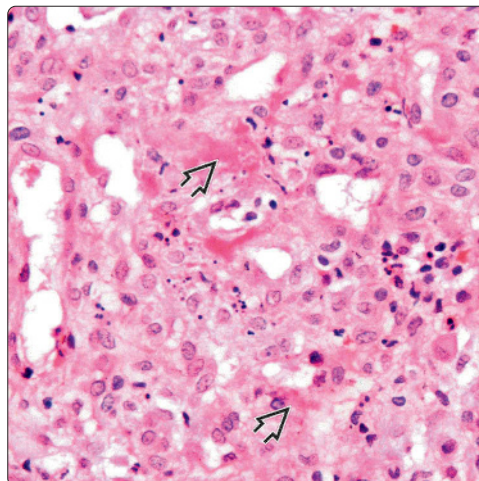


Blood Vessels and Neutrophils

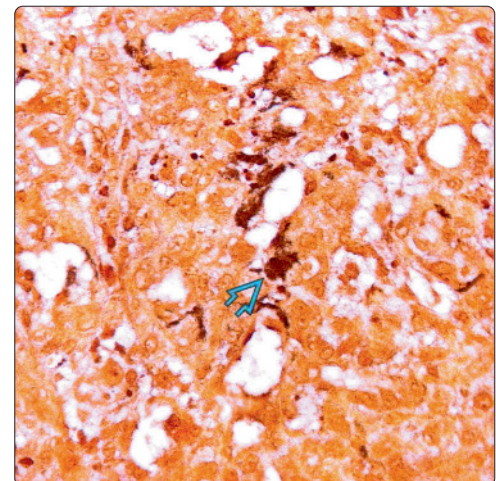


(Left) Clumps of granular purplish material of variable size positioned both interstitially and in the immediate vicinity of the vessels are diagnostic of BA. (Right) Numerous bacilli are best demonstrated by a modified silver staining (Warthin-Starry silver stain).

Lightly Basophilic Clumps

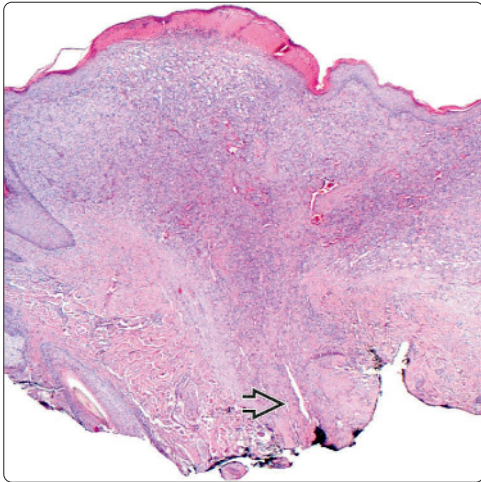


Bacilli in Lightly Basophilic Clumps on Silver Stain

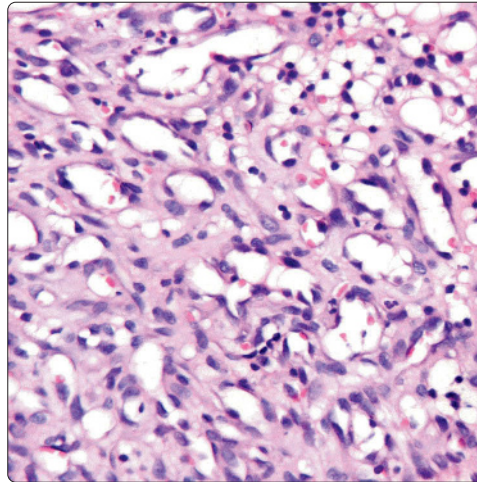




**Pyogenic Granuloma**

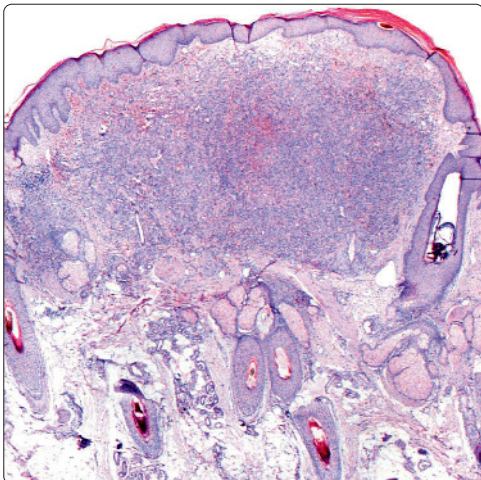


**No Nuclear Dust**

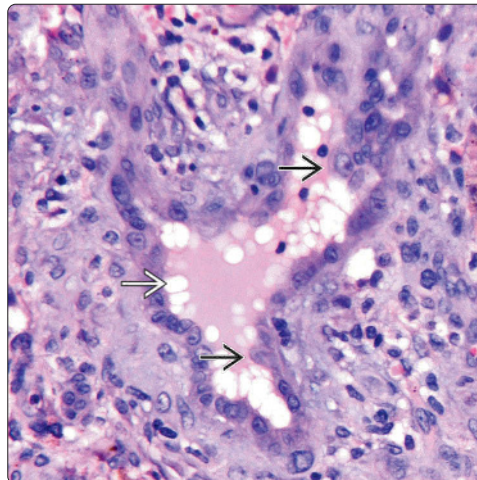


**(Left)** Ulcerated lobular proliferation of small vessels in an edematous stroma with a central feeder vessel [ ] are very characteristic of PG, as seen in this low-power view. **(Right)** Absence of nuclear dust of neutrophils and clumps of purplish granular material in a small blood vessel proliferation distinguishes PG from BA.

**Epithelioid Hemangioma**

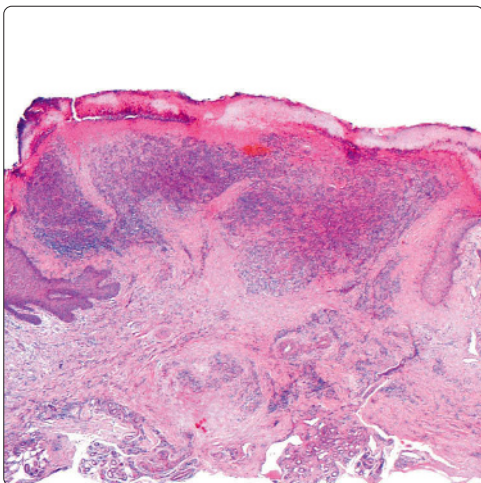


**Plump Endothelial Cells**

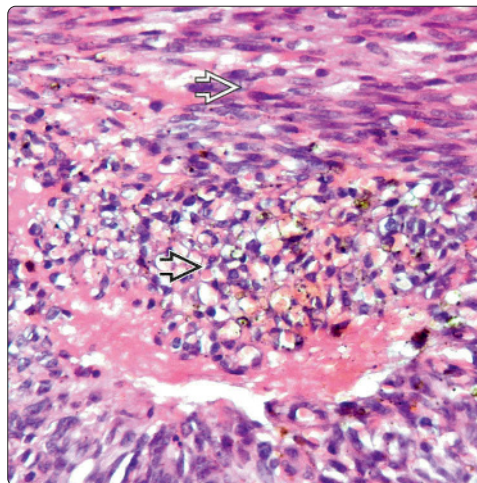


**(Left)** Scanning view of a well-circumscribed scalp lesion shows a vascular proliferation and a dense inflammatory infiltrate in another mimic of BA: Epithelioid hemangioma. **(Right)** Plump endothelial cells that protrude into the lumina of abnormal vessel (hobnail cells [ ]), some of them with intracytoplasmic vacuoles [ ], are diagnostic features of epithelioid hemangioma.

**Kaposi Sarcoma**



**Spindle Cell Proliferation**



**(Left)** Low-power view of a Kaposi sarcoma (KS) nodule from the hand shows an ulcerated, well-circumscribed, septate, lobular vascular proliferation. **(Right)** Close-up view shows the spindle cell proliferation with slit-like vascular spaces containing erythrocytes [ ] with the typical sieve-like appearance in cross section [ ] seen in KS.



# Nocardiosis and Actinomycosis

## KEY FACTS

### TERMINOLOGY

- Nocardiosis
  - Infection by gram-positive, weakly acid-fast bacteria that causes severe systemic illness often in immunocompromised patients and often pulmonary in origin
- Actinomycosis
  - Chronic bacterial infection usually of head and neck; rarely tongue, lips, gingivae, and buccal mucosae
- Infection by gram-positive, weakly acid-fast bacteria that causes severe systemic illness
- Nocardiosis
- Actinomycosis

### CLINICAL ISSUES

- Nocardiosis: Tumors or nodules that may follow lymphatics or cause draining sinus (mycetoma)
- Actinomycosis: Hard red-purple tumor on jaw that proceeds to abscess and produces yellow purulence (sulfur granules)

### MICROSCOPIC

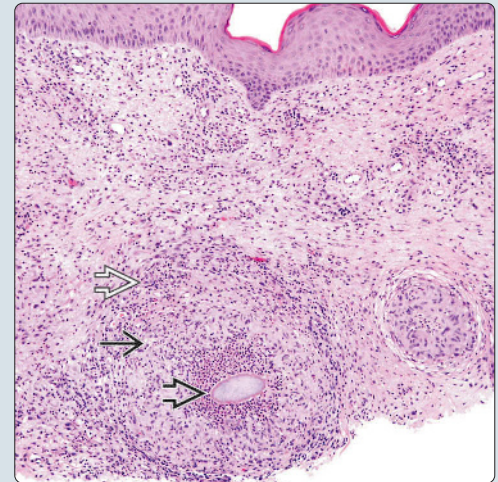
- Nocardiosis
  - Dense dermal and subcutaneous neutrophilic infiltrate with abscesses
  - Gram stain, methenamine silver, or partially acid-fast stain can help elucidate thin filamentous bacteria with right-angle branching
  - Sulfur granules in cases of mycetoma due to *Nocardia*
- Actinomycosis
  - Subcutaneous abscesses typically showing distinct lobules or nodules composed of mixed inflammatory cells
  - Characteristic sulfur granules (not pathognomonic) usually present surrounded by numerous neutrophils within nodules

**Sporotrichoid Spread of Nocardiosis**

(Left) Lymphocutaneous form of nocardiosis demonstrates a "sporotrichoid" spread starting as an ulcerative nodule on the middle finger and spreading along lymphatics to the middle hand. (Right) Low-power view from a patient with mycetoma due to *Nocardia* shows several nodules in the middermis with layered neutrophilic (suppurative) inflammation surrounding sulfur granules.

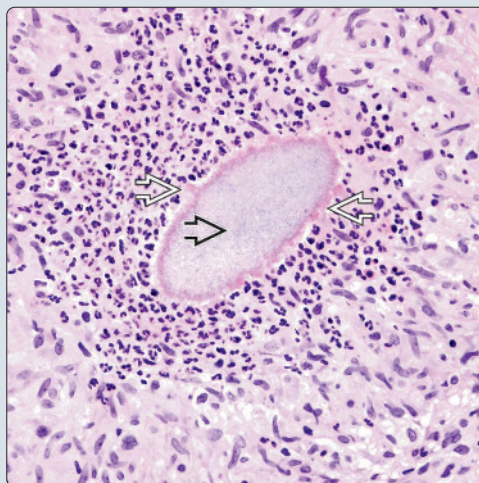


***Nocardia* Sulphur Granules**

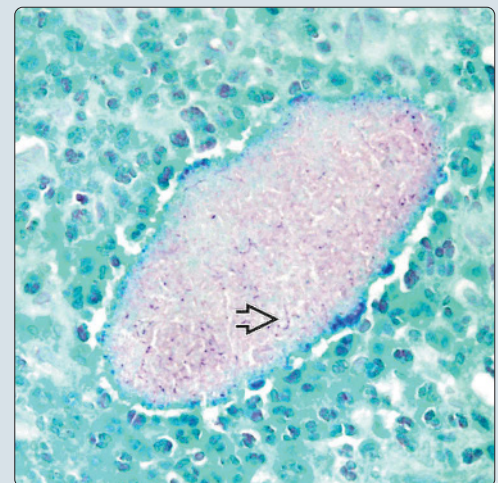


***Nocardia* With Surrounding Neutrophils**

(Left) This is a case of mycetoma due to *Nocardia* with numerous surrounding neutrophils. There are characteristic grains present with outer radiating eosinophilic projections that mimic the sulfur granule of actinomycosis. This was located in the middermis within a microabscess. (Right) This Gram stain of a mycetoma due to *Nocardia* demonstrates numerous small filamentous bacteria that are weakly gram positive.



***Nocardia* Is Weakly Gram Positive**





## TERMINOLOGY

### Synonyms

- Actinomycosis: Lumpy jaw

### Definitions

- Nocardiosis
  - Infection by gram-positive, weakly acid-fast bacteria that causes severe systemic illness
    - Often in immunocompromised patients and pulmonary in origin
- Actinomycosis
  - Chronic bacterial infection usually of head and neck; rarely tongue, lips, gingivae, and buccal mucosae

## ETIOLOGY/PATHOGENESIS

### Disseminated Form of Nocardiosis

- Caused by *Nocardia asteroides*
  - Skin disease present in 10% of cases
- Pulmonary infection disseminates
  - Seen in immunosuppressive states, such as organ transplants, AIDS, and myeloproliferative diseases

### Primary Cutaneous Form of Nocardiosis

- Caused by *Nocardia brasiliensis*
  - Infection follows penetrating injury or insect bite

### Actinomycosis

- Caused by *Actinomyces israelii*
  - Also normal inhabitant of nose and throat
  - Dental surgery, trauma, or abscess often precedes infection

## CLINICAL ISSUES

### Presentation

- Nocardiosis
  - Around 80% of affected patients are immunocompromised, and men are more often affected
  - Pulmonary nocardiosis most common (60%)
  - Skin and soft tissue infections 2nd most common form (21%)
  - Primary cutaneous form (5-12% of cases depending on study)
    - Tumors or nodules that may follow lymphatics or cause discharging sinuses as in mycetoma (Madura foot)
    - Also ulcers or cellulitis
  - Disseminated form: Vesiculopustules or abscesses
- Actinomycosis
  - Hard red-purple tumor on jaw proceeds to abscess and produces yellow purulence (sulfur granules)
  - Rarely forms on chest wall from underlying lung infection

### Treatment

- Nocardiosis
  - Trimethoprim/sulfamethoxazole 1st choice
  - 2nd choice
    - Amoxicillin clavulanate (for *N. brasiliensis*)
    - Minocycline (for *N. asteroides*)
- Actinomycosis

- Penicillin 1st choice with erythromycin or doxycycline if allergic to penicillin
  - Surgical debridement of sinus tract is important

### Prognosis

- Nocardiosis
  - Systemic or pulmonary
    - Overall mortality 25% in one study (mainly in patients with pulmonary involvement)
  - Primary cutaneous
    - Excellent
- Actinomycosis
  - Excellent with proper treatment
  - Rare development of meningitis

## MICROSCOPIC

### Histologic Features

- Nocardiosis
  - Dense dermal and subcutaneous neutrophilic infiltrate with abscesses
  - Nonspecific granulomatous inflammation is also usually present
  - Older lesions may show more chronic inflammation
  - Gram stain, methenamine silver, or partially acid-fast stain can help elucidate thin filamentous bacteria with right-angle branching
- Actinomycosis
  - Subcutaneous abscesses typically showing distinct lobules or nodules composed of mixed inflammatory cells
  - Characteristic sulfur granules (not pathognomonic) usually present surrounded by numerous neutrophils within nodules
    - Center is composed of basophilic filamentous actinomycete bacteria
    - Periphery of sulfur granule has radiate, intensely eosinophilic projections around bacteria (Splendore-Hoeppli phenomenon)
    - Splendore-Hoeppli phenomenon is not specific for actinomycosis or even fungal infections in general

## ANCILLARY TESTS

### Gram Stain

- *Nocardia* are gram-positive thin filamentous bacilli with right-angle branching
- Actinomycotic lesions will have gram-negative stain in periphery (acidophilic projections)
  - Beaded filaments at periphery of granules are gram positive

### Gomori Methenamine Silver Stain

- Will stain both *Nocardia* and *Actinomyces* species
- Stain organisms gray-black in color

### Modified Acid-Fast Stain

- All 3 species of *Nocardia* are partially acid fast

### Periodic Acid-Schiff Stain

- Will stain *Actinomyces* organisms bright pink

## DIFFERENTIAL DIAGNOSIS

### Histologic Differential Diagnosis for Nocardiosis and Actinomycosis

- **Infectious suppurative granulomatous dermatoses**
  - Careful search for infectious organisms on high power may reveal characteristic morphology
  - Noninfectious causes include pyoderma gangrenosum, ruptured cysts, or follicles
- **Sporotrichosis**
  - Pseudoepitheliomatous hyperplasia often with hyperkeratosis and occasionally parakeratosis
  - Dermal granulomatous inflammation with occasional microabscess formation and multinucleated giant cells
  - Sporothrix asteroid bodies (globose basophilic cells with radiating eosinophilic rays) or yeast forms may be seen on H&E-, Gomori methenamine silver (GMS)-, or periodic acid-Schiff (PAS)-stained sections
- **Blastomycosis**
  - Pseudoepitheliomatous hyperplasia (PEH) with microabscesses, granulomatous inflammation, and giant cells
  - Broad-based budding yeasts (7-15 µm) are characteristic
- **Coccidioidomycosis**
  - PEH with granuloma formation
  - Large, mature, thick-walled spherules (10-80 µm) sometimes with smaller endospores are often easily seen in H&E sections
- **Paracoccidioidomycosis**
  - PEH with granulomas and acute and chronic inflammation with suppuration occasionally
  - Only found in South America
  - Characteristic budding yeasts with mariner's wheel configuration easily seen with GMS stain
- **Chromomycosis**
  - Characteristic "copper pennies" (medlar or sclerotic bodies) seen on H&E sections
  - PEH, hyperkeratosis
  - Dermal granulomas and microabscesses with characteristic thick-walled sclerotic bodies
- **Phaeohyphomycosis**
  - Central cyst with inflammation and necrotic debris and granulomatous inflammation surrounding
  - Characteristic pigmented hyphae (fungal elements) within cystic cavity
  - Often wood splinter also identified on sections
- **Eumycetoma**
  - "Eu" meaning caused by "true" fungi vs. actinomycetomas caused by bacteria
  - Characteristic grains amidst sea of neutrophils (suppurative inflammation) along with tumefaction, draining sinuses, and abscess formation
    - 2-4-µm segmented hyphae ("grains") are usually brown (black grains) or white/yellow (pale grains) on H&E stains
    - Splendore-Hoeppli phenomenon may be seen surrounding grains
  - *Nocardia* and *Actinomadura* spp. can cause almost indistinguishable picture histologically (actinomycetomas)
    - Gram stain will identify characteristic small (< 1 µm) thin filamentous bacteria that cause actinomycetomas
    - Grains are typically homogeneously eosinophilic, gram positive
    - Culture necessary to guide treatment
- **Botryomycosis**
  - Rare pseudomycotic bacterial disease with small white granules among numerous neutrophils (suppurative inflammation) and granulomatous inflammation
    - Granules may appear very similar to actinomycosis
  - Gram stain can help identify causative bacteria (*Staphylococcus aureus* most common)
  - Culture may be necessary to rule out fungal etiology and determine causative bacteria
- **Cat scratch disease**
  - PEH with underlying stellate granulomas and giant cells in dermis
  - Necrosis, fibrin, neutrophils, and prominent karyorrhexis in dermis with surrounding mantle of chronic inflammation
  - Causative, small, gram-negative bacilli (*Bartonella henselae* or other) can be found within macrophages and in areas with florid neutrophils and necrosis
  - Warthin-Starry or Brown-Hopps stain may be helpful in demonstrating organisms
- **Noninfectious mimics**
  - Pyoderma gangrenosum
    - Characteristic rolled edges clinically
    - Deep, well-demarcated ulcer
    - Neutrophils at edges of ulcer undermining intact dermis
    - Often underlying systemic disease
    - No organisms identified by special stains
  - Ruptured cyst
    - Often dense chronic active inflammation with foreign body giant cells
    - Granulomatous reaction and hypervascularity
    - No organisms identified by special stains

### Clinical Differential Diagnosis for Nocardiosis

- **Sporotrichosis**
  - Lymphocutaneous form of *Nocardia* may mimic
  - Sulfur granules not present
  - Culture may be necessary to distinguish

### Clinical Differential Diagnosis for Actinomycosis

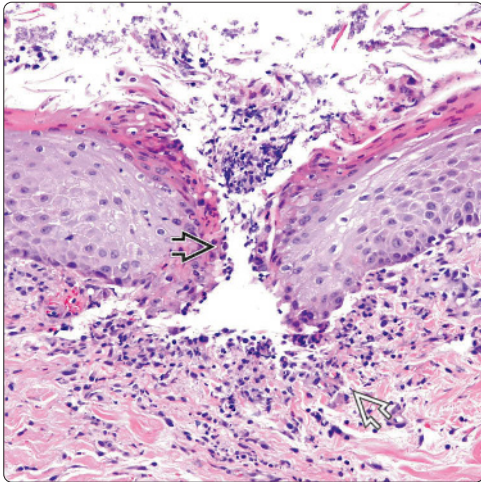
- **Draining dental abscess**
  - History of dental procedure
- **Squamous cell carcinoma**
  - Older patient with markedly photodamaged skin
  - No abscess formation with indurated, irregular border
  - Surface keratotic, ulcerated, or covered with exudate (serous or hemorrhagic)

## SELECTED REFERENCES

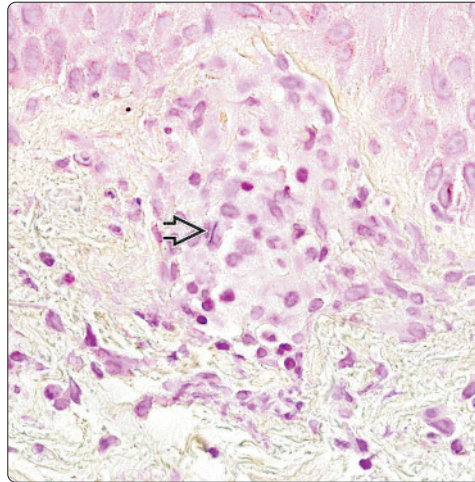
1. Abreu C et al: Nocardia infections among immunomodulated inflammatory bowel disease patients: A review. *World J Gastroenterol.* 21(21):6491-8, 2015
2. Hardak E et al: Clinical spectrum and outcome of Nocardia infection: experience of 15-year period from a single tertiary medical center. *Am J Med Sci.* 343(4):286-90, 2012
3. Ngow HA et al: Cutaneous actinomycosis: the great mimicker. *J Clin Pathol.* 62(8):766, 2009



**Cutaneous Ulcer**



**Filamentous Bacteria**

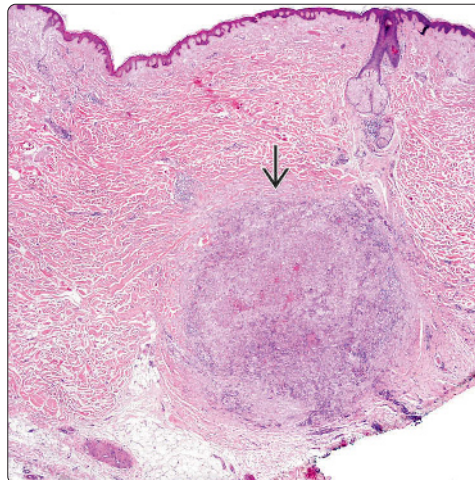


(Left) This case of cutaneous nocardiosis shows a focal ulcer [box] with mixed granulomatous dermal inflammation [box]. A Gram stain demonstrated characteristic rod-shaped, weakly gram-positive organisms. (Right) A Gram stain of this case of cutaneous nocardiosis demonstrates a single characteristically rod-shaped, weakly gram-positive bacterium [box].

**Cervicofacial Actinomycosis**

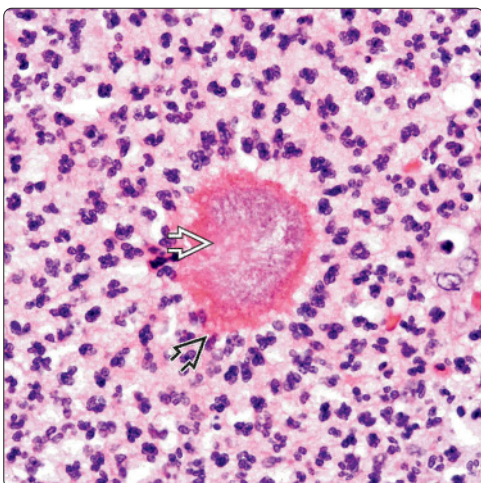


**Deep Dermal Abscess**

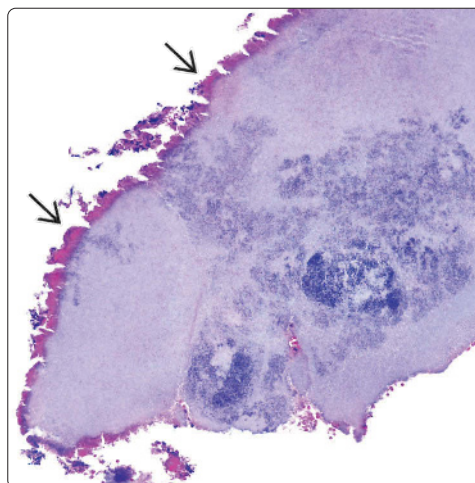


(Left) This is the typical presentation of cervicofacial actinomycosis with hard red-purple abscesses in the jaw ("lumpy jaw") due to *Actinomyces israelii* and missed antibiotic treatment. (Courtesy J. Ervens, MD.) (Right) This low-power view of actinomycosis demonstrates a distinct deep dermal abscess nodule [box] bordering subcutaneous tissue. Nocardia presents similarly as deep dermal, often subcutaneous abscesses.

**Actinomyces Sulphur Granule**



**Splendore-Hoepli Phenomenon in Actinomycosis**

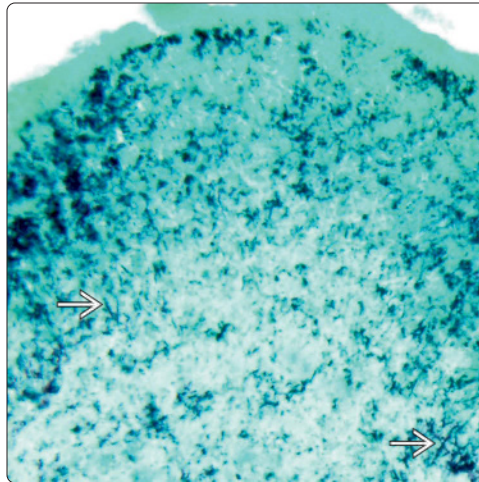


(Left) Histology of actinomycosis on high power demonstrates the characteristic sulfur granule centrally composed of filamentous bacteria [box] and peripheral radiating eosinophilic projections [box]. (Right) Sulfur granules from actinomycosis can sometimes be quite large. In this specimen, the epidermis was not present. Note the radiating eosinophilic projections [box].

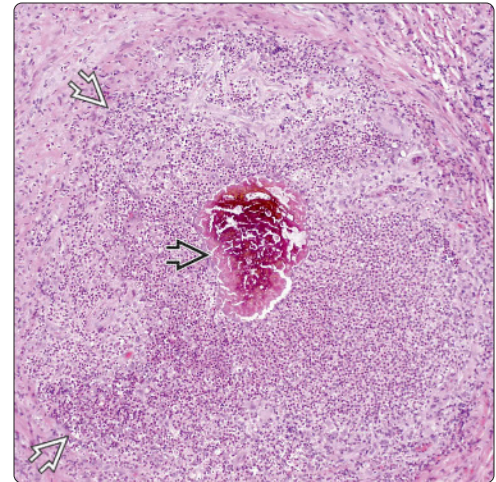


(Left) GMS of a large actinomycotic sulfur granule stains the filamentous bacteria black. (Right) Higher power view shows eumycetoma caused by fungi. Note the surrounding suppurative neutrophilic infiltrate. The grains of eumycotic mycetoma typically appear black or pale. (Courtesy B. Pitt, MD.)

GMS-Positive Filamentous Bacteria

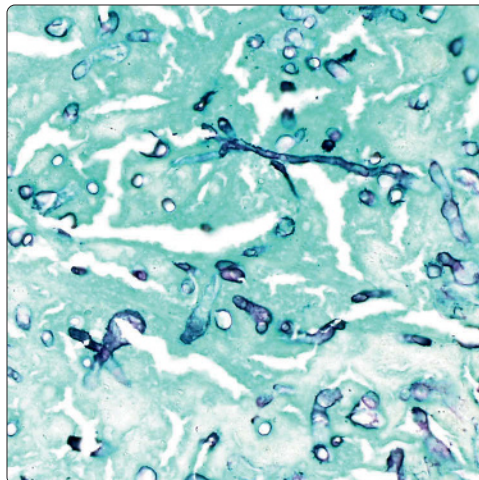


Eumycetoma

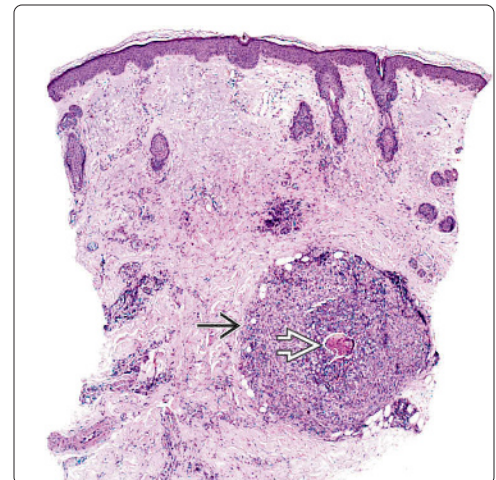


(Left) Branched fungal hyphae are present on this GMS stain. The hyphae are broad and septate with 45° branching, suspicious for Aspergillus. (Right) Botryomycosis can show a similar dermal nodule composed of suppurative granulomatous inflammation. The granule in the center of the inflammation can mimic actinomycosis but is composed of different bacteria than actinomycosis.

Fungal Appearance With GMS

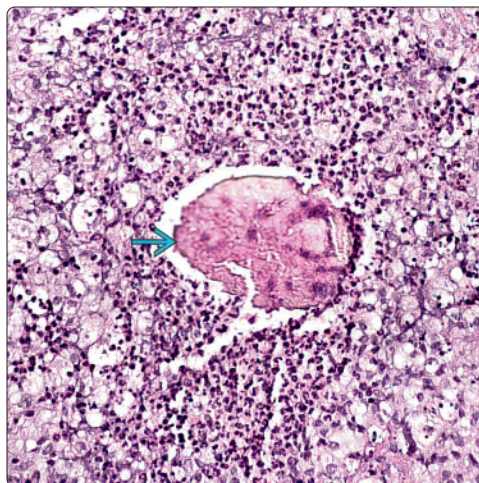


Botryomycosis With Dermal Granulomatous Inflammation

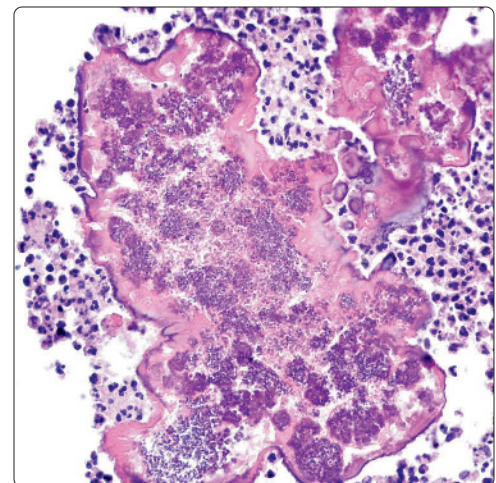


(Left) High-power view of botryomycosis shows a small granule surrounded by neutrophils and histiocytes. A GMS stain would be negative for filamentous bacteria, such as Nocardia or actinomycosis, and a Gram stain would highlight bacteria within the granule. (Right) High-power view of botryomycosis shows numerous bacterial organisms in the center of suppurative neutrophilic inflammation. A Gram stain would help differentiate this from sulfur granules of actinomycosis or nocardiosis.

Botryomycosis Granule



Numerous Nonfilamentous Bacteria

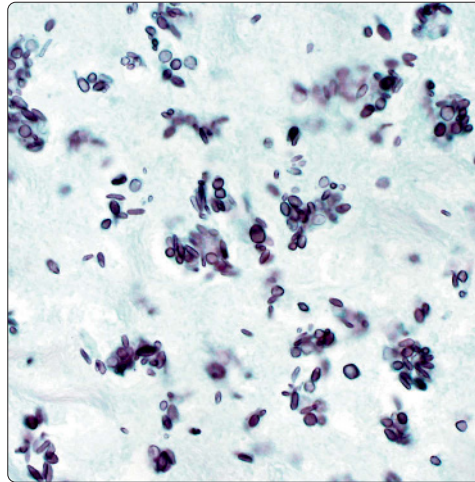




**Sporotrichoid Spread in Cutaneous Sporotrichosis**

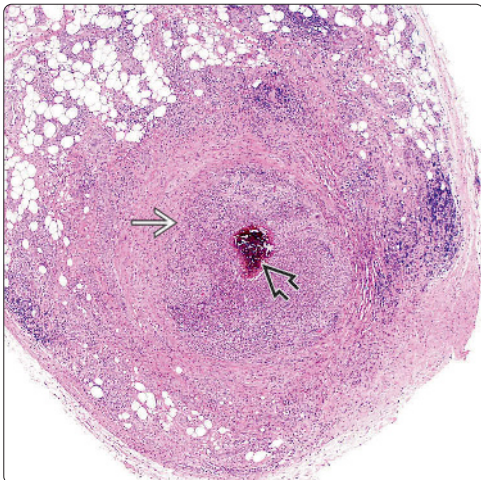


**Sporothrix Yeast**

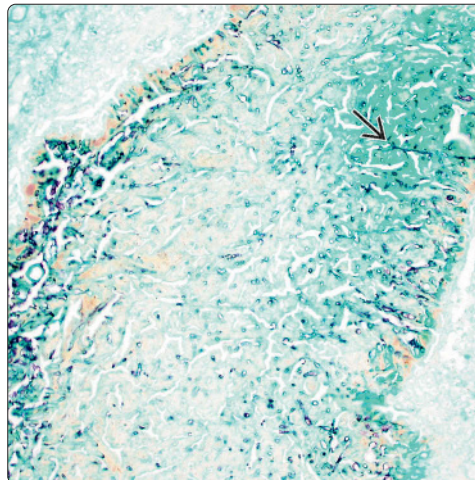


(Left) This city gardener presented with a several-month history of enlarging asymptomatic nodules moving proximally up his arm, which cultured sporotrichosis and responded to oral potassium iodide. (Right) Routine H&E, PAS, or GMS may demonstrate the yeast forms of *Sporothrix* species in tissue sections. These yeasts were identified within nodules in the subcutaneous tissue of a skin biopsy specimen with a GMS stain. (Courtesy B. Pritt, MD.)

**Fungal Eumycetoma**

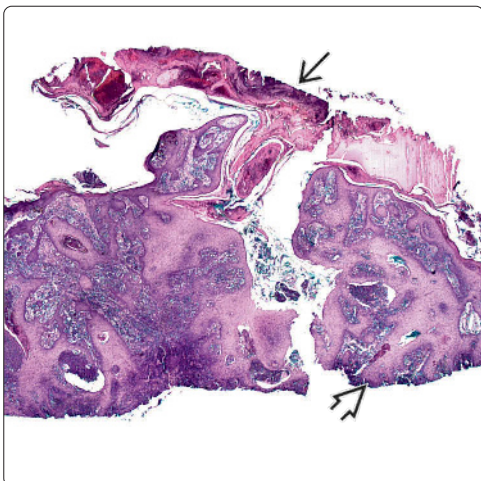


**GMS-Positive Fungal Elements in Eumycetoma**

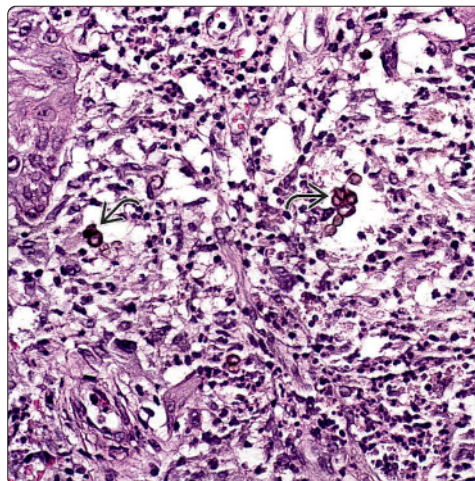


(Left) Eumycotic mycetoma (eumycetoma) can have a similar histological appearance to actinomycetoma. This case presented as a draining tract in the subcutaneous tissue with suppurative inflammation surrounding the characteristic black grains (brown on H&E). (Right) Eumycetoma demonstrates numerous fungal elements within a draining sinus tract in the subcutaneous tissue on GMS. (Courtesy B. Pritt, MD.)

**Pseudoepitheliomatous Hyperplasia in Chromomycosis**



**Round Fungal Cells of Chromomycosis**



(Left) This shave biopsy of chromomycosis demonstrates pseudoepitheliomatous hyperplasia (PEH) with hyperkeratosis and dermal granulomatous inflammation. Actinomycosis and nocardiosis typically do not have PEH. (Right) High-power view of a biopsy specimen of chromomycosis demonstrates the characteristic thick-walled, dark brown, round to polyhedral muriform fungal cells called medlar/sclerotic bodies or "copper pennies."



## Rocky Mountain Spotted Fever

## KEY FACTS

## TERMINOLOGY

- Potentially fatal, multiorgan vasculitic disorder with clinical triad of fever, headache, and rash
  - Caused by *Rickettsia rickettsii*

## CLINICAL ISSUES

- Early phase: 2-14 days post tick bite; fever, headache, nausea/vomiting
- Skin manifestations: 2-5 days post fever; centripetal spread of macules & papules; ± petechiae/purpura
- Diagnosis/treatment: History, exam, & epidemiology
- Treatment delay: Significant morbidity & mortality
- Fatal outcome: 20-23% untreated, 5% treated
- Factors indicating poor prognosis: Age < 4 years or > 60 years, > 5 days between onset & treatment, nontetracycline treatment, no history of tick bite, delayed rash, G6PD deficiency, hepatomegaly, jaundice, CNS/renal deficits

## MICROSCOPIC

- Early: Lymphocytic vasculitis; late: leukocytoclastic vasculitis ± fibrin thrombi
- Late: Leukocytoclastic vasculitis ± fibrin thrombi
- Early & late: Endothelial cell swelling, dermal edema, red blood cell (RBC) extravasation ± vacuolar interface dermatitis, necrotic keratinocytes, lymphocyte exocytosis ± epidermal necrosis

## TOP DIFFERENTIAL DIAGNOSES

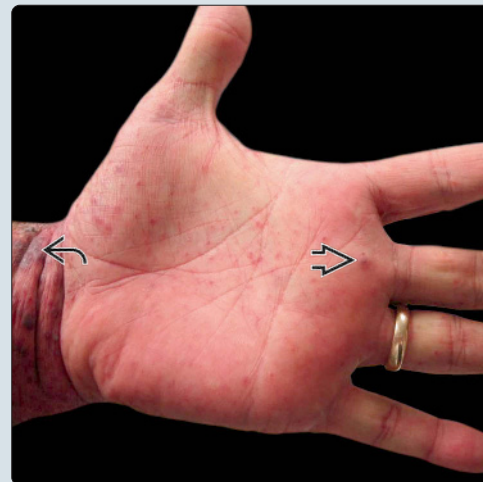
- Disseminated intravascular coagulation
- Non-RMSF septic vasculitis
- Collagen vascular disease-related vasculitis
- Mixed cryoglobulinemia

## Scattered Red Macules and Papules

(Left) Rocky Mountain spotted fever (RMSF) involving the axilla shows scattered red macules and papules, some of which are surmounted by a central red crust. (Courtesy A. McClung, MD.) (Right) This image of RMSF shows red macules and papules with admixed petechiae involving the palm. Crusted purpuric macules and papules involving the wrist are also noted. (Courtesy A. McClung, MD.)

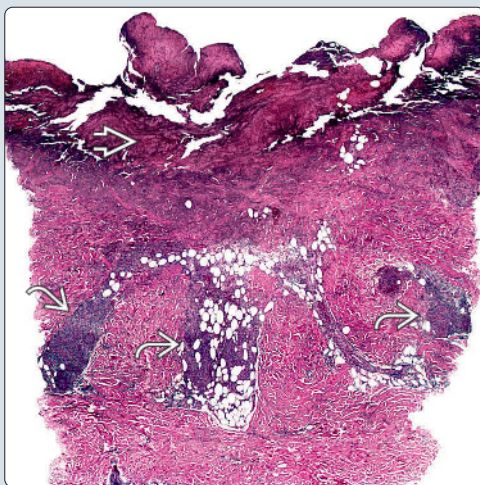


## Red Macules and Papules on Palm

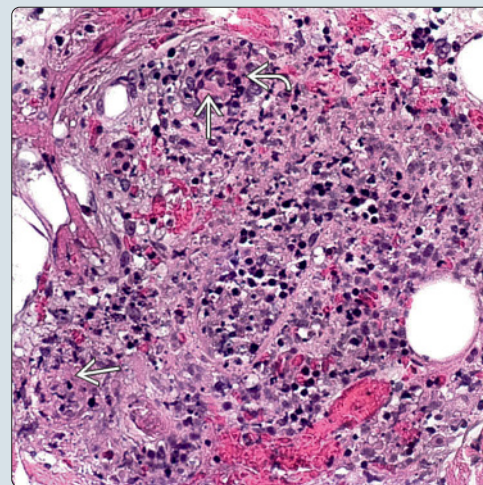


## Ulceration With Pan-Dermal Inflammation

(Left) In this low-power view of RMSF, there is a dense pan-dermal perivascular and interstitial inflammatory infiltrate extending into subcutis. Ulceration is noted. (Right) Higher power view of a biopsy from a rash of RMSF shows a predominantly lymphocytic vasculitis with intraluminal thromboses.



## Lymphocytic Vasculitis With Thromboses





## TERMINOLOGY

### Abbreviations

- Rocky mountain spotted fever (RMSF)

### Definitions

- Rickettsiosis represents group of tick-borne diseases caused by *Rickettsia* spp.
- RMSF is potentially fatal, multiorgan, vasculitic disorder characterized by classic clinical triad of fever, headache, and rash
  - Caused by *Rickettsia rickettsii*

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- R. rickettsii*: Intracellular, gram-negative coccobacilli
  - Reservoir & vectors: Ixodidae Family (hard ticks)
    - Dermacentor variabilis*: Eastern 2/3 of USA;
    - Dermacentor andersoni*: Pacific coast of USA; *R. sanguineus*: SW USA, Mexico, Central America
  - Transmission: Feeding tick injects saliva mixed with bacteria into bloodstream of human host
    - R. rickettsii* multiplies within endothelial cells of small- to medium-sized blood vessels

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Late spring and early summer
  - Endemic: Rural/suburban SW/MW USA, South America

### Presentation

- Early phase: 2-14 days post tick bite
  - Nonspecific symptoms: Fever ( $> 38.9^{\circ}\text{C}$ ), severe headache, GI/constitutional symptoms
- Cutaneous manifestations: 2-5 days post fever
  - Centripetal spread from wrists/ankles, to palms/soles, then trunk/proximal extremities
  - Lesions: Macules then papules;  $\pm$  petechiae/purpura (35-60%);  $\pm$  necrosis/gangrene (4%)
  - Cutaneous findings absent in 10%

### Laboratory Tests

- Nonspecific: Anemia, thrombocytopenia, hyponatremia, increased liver function tests, and creatine kinase

### Treatment

- Initiate treatment when RMSF is clinically suspected, particularly in endemic areas
- Best outcome if treated within first 5 days of symptoms
- Tetracyclines & chloramphenicol: Only proven treatment
  - Doxycycline is drug of choice for adults and children; chloramphenicol is 2nd choice
  - Severe disease: Longer/intravenous treatment; inpatient
- Proper tick removal
- Failed response to treatment suggests incorrect diagnosis
- Prophylactic treatment after tick bite not recommended

### Prognosis

- Fatal outcome: 20-23% untreated, 5% treated

- Factors indicating a poor prognosis: Age  $< 4$  years or  $> 60$  years,  $> 5$  days between onset & treatment, nontetracycline treatment, no history of tick bite, delayed rash, G6PD deficiency, hepatomegaly, jaundice, CNS/renal deficits

## MICROSCOPIC

### Histologic Features

- Early: Perivascular lymphocytes  $\pm$  vasculitis
- Late: Leukocytoclastic vasculitis  $\pm$  fibrin thrombi
- Early & late: Endothelial cell swelling, dermal edema, red blood cell (RBC) extravasation  $\pm$  vacuolar interface dermatitis, necrotic keratinocytes, lymphocyte exocytosis  $\pm$  epidermal necrosis

## ANCILLARY TESTS

### Immunohistochemistry

- Immunoperoxidase techniques demonstrate *R. rickettsii* in vessel wall/endothelium

### Immunofluorescence

- Fluorescein-labeled antisera demonstrates *R. rickettsii* in vessel wall/endothelium

### PCR

- Limited diagnostic value given scarce circulating *R. rickettsii* organisms in early disease

### Serologic Testing

- Indirect fluorescent antibody test: Gold standard
  - Highly sensitive but not specific: Cannot distinguish between *R. rickettsii* and other spotted fever group rickettsiae

## DIFFERENTIAL DIAGNOSIS

### Disseminated Intravascular Coagulation

- Clinical: Similar to RMSF; no centripetal spread
- Laboratory: Decreased protein C/S/antithrombin
- Histopathologic: Vessel thrombosis, minimal inflammation/no vasculitis, epidermal necrosis

### Non-RMSF Septic Vasculitis

- Clinical: Similar to RMSF; no centripetal spread
- Laboratory: (+) blood, CSF, urine, or sputum cultures
- Histopathologic: Indistinguishable from late RMSF  $\pm$  intraepidermal pustules

### Collagen Vascular Disease-Related Vasculitis

- Clinical: Similar to RMSF; malar rash, arthritis
- Laboratory: (+) ANA, rheumatoid factor
- Histopathologic: Indistinguishable from late RMSF  $\pm$  dermal mucin  $\pm$  lupus band test

### Mixed Cryoglobulinemia

- Clinical: Similar to RMSF; no centripetal spread
- Laboratory: (+) mixed cryoglobulins, ant-hepatitis C Ab
- Histopathologic: Indistinguishable from late RMSF

## SELECTED REFERENCES

- Woods CR: Rocky Mountain spotted fever in children. *Pediatr Clin North Am*. 60(2):455-70, 2013

## Rhinoscleroma

## KEY FACTS

## ETIOLOGY/PATHOGENESIS

- *Klebsiella pneumoniae* subspecies *rhinoscleromatis*

## CLINICAL ISSUES

- Rare and chronic condition that affects nasopharyngeal mucosa
- 3 stages are present during disease progression: Catarrhal, granulomatous, and sclerotic

## MICROSCOPIC

- Slight acanthosis to pseudoepitheliomatous hyperplasia with extensive necrosis
- Diffuse inflammatory granulomatous infiltrate predominantly of mononuclear cells, plasma cells, and histiocytes, filling stroma
- Mikulicz cells: Large, rounded, and vacuolated histiocytes with pale-colored, reticulated, and ill-defined cytoplasm and eccentric nucleus
  - Gram-negative bacilli can be identified intracellularly

- Russell bodies: Anucleated eosinophilic intracytoplasmic structures derived from plasma cells

## TOP DIFFERENTIAL DIAGNOSES

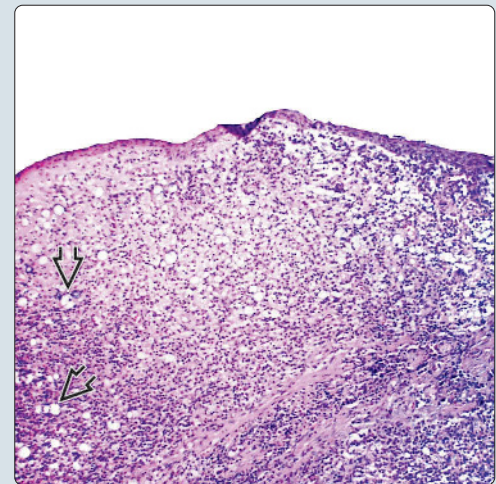
- Granuloma Inguinale
  - Clinically affects different location (typically ulcerative genital lesions)
  - Different organism (*Klebsiella granulomatis*) but similar morphology
- Histoplasmosis
  - Organisms are round (vs. bacilli of rhinoscleroma)
  - Geographically in different locations
- Leprosy
  - Clinical presentation is much different
    - Hypoesthesia, skin lesions, and peripheral neuropathy
  - Organisms smaller (difficult to visualize on H&E stain) and positive with mycobacterial stains (AFB, Fite)

Nasal Deformity With Ulcerated Hard Palate

(Left) Clinically, rhinoscleroma can result in striking nasal deformity, septal deviation, and nasal obstruction [E]. Rhinoscleroma can also demonstrate an ulcerated hard palate with granulomatous areas [E]. (Right) Low-power view of rhinoscleroma demonstrates a diffuse inflammatory infiltrate in the underlying submucosa. Large foamy macrophages (Mikulicz cells) [E] can be appreciated even at this power.

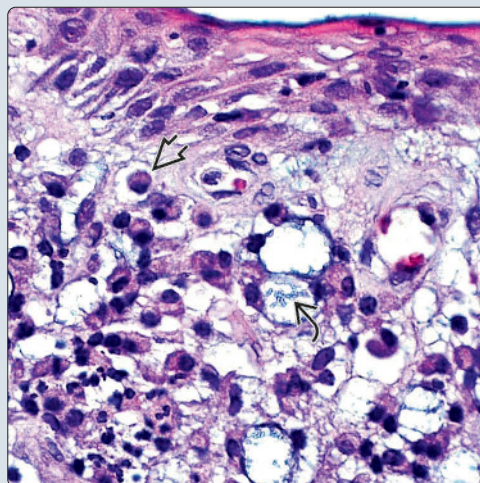
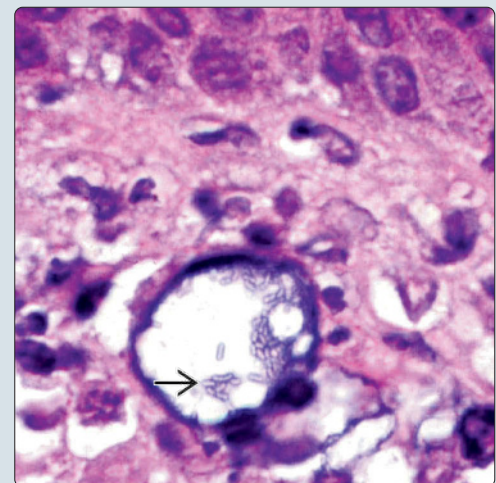


Diffuse Submucosal Inflammatory Infiltrate With Foamy Cells



Numerous Mikulicz Cells With Plasma Cell Infiltrate

(Left) Mikulicz cells here are mixed with numerous plasma cells [E]. Bacilli [E] can be seen within Mikulicz cells even from this power. (Right) Numerous bacilli [E] of *Klebsiella pneumoniae* subspecies *rhinoscleromatis* can be seen within this Mikulicz cell on high power.

Bacilli of *Klebsiella* Within Mikulicz Cell



**TERMINOLOGY****Synonyms**

- Respiratory scleroma

**Definitions**

- Rare chronic granulomatous infection that affects nose and respiratory tract
- Caused by capsulated gram-negative bacterium, *Klebsiella pneumoniae* subspecies *rhinoscleromatis*

**ETIOLOGY/PATHOGENESIS****Unclear**

- Infection by direct or indirect contact with patient during catarrhal stage
- *Klebsiella pneumoniae* subspecies *rhinoscleromatis* shows predilection for rhinopharyngeal mucous
- Cellular immunity is probably impaired
  - CD4:CD8 ratio in lesions is altered with decreased levels of CD4 lymphocytes
- Macrophages are not fully activated
  - Retain bacilli within vacuoles but are unable to destroy them

**CLINICAL ISSUES****Epidemiology**

- Incidence
  - Rare disease
- Age
  - Typically affects patients in 2nd or 3rd decade of life
- Sex
  - F:M = 13:1
- Ethnicity
  - Most cases have been reported from Central Africa, Central and South America, Eastern and Central Europe, Middle East, India, and Indonesia

**Site**

- Nasal or nasopharyngeal involvement is seen in 95-100% of patients
- Extension to larynx, trachea, nasolacrimal duct, and premaxilla has been reported

**Presentation**

- Disease progress in 3 overlapping stages
  - Catarrhal stage: Nonspecific rhinitis symptoms, fetid rhinorrhea, crusting, and nasal obstruction
  - Granulomatous stage: Hypertrophic granulation tissue with scabs and progressive hardening of affected tissues leading to nasal deformity known as nose of Hebra (tapir nose)
  - Sclerotic stage: Extensive scarring and nasal vestibular stenosis

**Prognosis**

- Chronic disease with very slow course, clinical remissions, and very frequent relapses
- Disease can be fatal due to airway obstruction or intracranial invasion

**MICROSCOPIC****Histologic Features**

- Slight acanthosis to pseudoepitheliomatous hyperplasia with extensive necrosis
- Diffuse inflammatory granulomatous infiltrate predominantly of mononuclear cells, plasma cells, and histiocytes, filling stroma
- Mikulicz cells: Large, rounded, and vacuolated histiocytes with pale-colored, reticulated, and ill-defined cytoplasm and eccentric nucleus
  - Gram-negative bacilli can be identified intracellularly
- Russell bodies: Anucleated eosinophilic intracytoplasmic structures derived from plasma cells

**ANCILLARY TESTS****Laboratory Studies**

- Bacterial isolation by culture on blood or MacConkey agar is positive in 1/2 of cases
- Bacilli can be highlighted in lesions with PAS, Giemsa, or Warthin-Starry special stains
- Immunoperoxidase staining using *Klebsiella* capsular type 3 antiserum
- PCR assay has been tried in animals but is not yet approved for human use

**DIFFERENTIAL DIAGNOSIS****Other Infectious Granulomatous Processes and Neoplasms**

- Histopathologic
  - Granuloma Inguinale
    - Clinically affects different location (typically ulcerative genital lesions)
    - Different organism (*Klebsiella granulomatis*) but similar morphology
      - ◻ Intracellular bacilli (Donovan bodies) identified with Wright-Giemsa or Warthin-Starry stain
  - Histoplasmosis
    - Organisms are round (vs. bacilli of rhinoscleroma)
    - Geographically in different locations
      - ◻ Histoplasmosis found mainly in the Midwestern United States (Ohio and Mississippi River Valleys)
  - Leprosy
    - Clinical presentation is much different
      - ◻ Hypoesthesia, skin lesions, and peripheral neuropathy
      - ◻ Numerous different clinical types (tuberculoid, lepromatous, indeterminate, others)
    - Organisms smaller (difficult to visualize on H&E stain) and positive with mycobacterial stains (AFB, Fite)

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## KEY FACTS

### ETIOLOGY/PATHOGENESIS

- *Streptococcus pyogenes* is frequently identified as causative organism

### CLINICAL ISSUES

- Usually occurs in warmer climates
- Lower limbs most frequent
- Lesions may be up to 1-2 cm
- Well-circumscribed ulcers with thick, adherent crust
  - Punched-out ulcers
- Resolution of lesions leads to scarring
- Age
  - Children are most commonly affected
- Sex
  - Both sexes affected equally
- Ethnicity
  - No race predilection
- Treatment
  - Topical and systemic antibiotics are useful

### MICROSCOPIC

- Abrupt ulceration, usually with heavy neutrophil inflammation
- Granulation tissue may be present
- Adjacent epidermis may be thickened, but there is no undermining by ulcer edge
- Thick overlying purulent serum crust
- With chronicity, there may be increased amounts of fibrosis and scarring at ulcer edges

### ANCILLARY TESTS

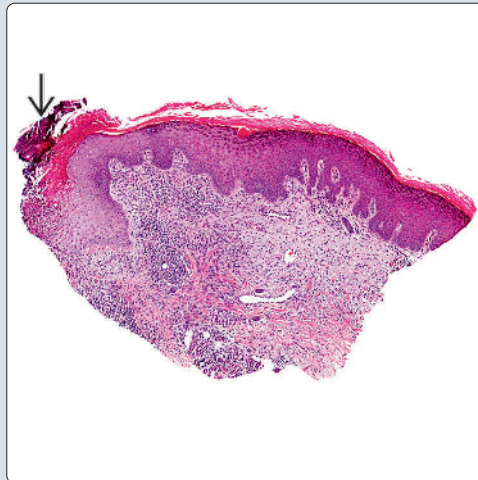
- Gram stain, wound or tissue cultures

### TOP DIFFERENTIAL DIAGNOSES

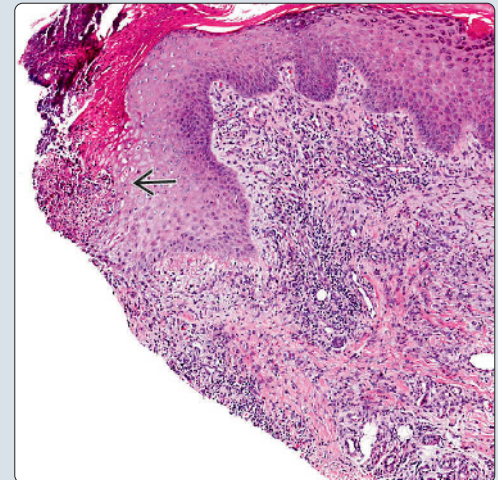
- Impetigo
- Trauma/prurigo
- Stasis ulceration
- Pyoderma gangrenosum
- Calciphylaxis

#### Inflammation and Crusting

(Left) At low power, the overlying crust is evident [A]. There is increased cellularity in the dermis as well, indicative of an inflammatory cell infiltrate. (Right) There is ulceration at the edge of the biopsy [B]. The underlying inflammatory cell infiltrate is directly associated with this epidermal disruption.

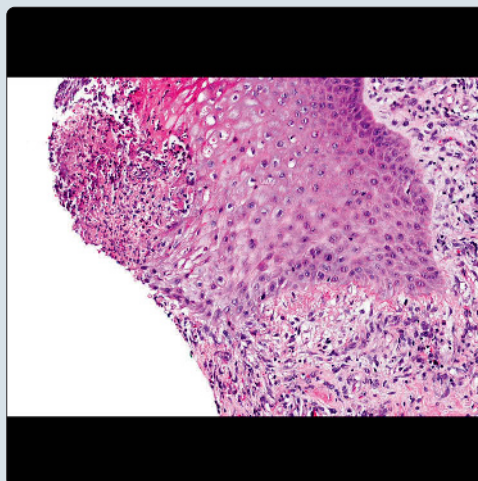


#### Ulceration Is Present

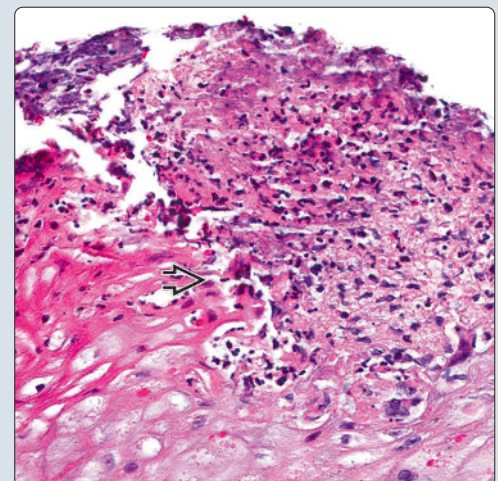


#### Neutrophil Inflammation

(Left) The area of ulceration beneath the crusting has necrotic debris and numerous neutrophils, which extend through the epidermis into the dermis. (Right) The edge of the ulceration is well circumscribed and abrupt, which gives a clinical appearance of a punched-out ulcer [C]. A Gram stain may be able to demonstrate causative bacteria in this area.



#### Punched-Out Edge of Ulcer





## TERMINOLOGY

### Definitions

- Punched-out ulceration, predominantly on lower limbs, with thick adherent crust

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- *Streptococcus pyogenes* is frequently identified as causative organism

## CLINICAL ISSUES

### Epidemiology

- Age
  - Children are most commonly affected
  - All ages may be affected
- Sex
  - Both sexes affected equally
- Ethnicity
  - No race predilection

### Presentation

- Usually occurs in warmer climates
- Lower limbs most frequent
  - Other sites may also be involved
  - Trauma, scabies infection, or other factors may determine which site(s) is(are) affected
- Lesions may be up to 1-2 cm
  - May be larger in particularly severe cases
- Well-circumscribed ulcers with thick, adherent crust
  - Punched-out ulcers
- Pain may be feature
- Resolution of lesions leads to scarring

### Treatment

- Topical and systemic antibiotics are useful

### Prognosis

- Complete resolution with appropriate therapy

## MICROSCOPIC

### Histologic Features

- Abrupt ulceration, usually with heavy neutrophil inflammation
  - Often with admixed lymphocytes
- Granulation tissue may be present
- Adjacent epidermis may be thickened, but there is no undermining by ulcer edge
- Thick overlying purulent serum crust
- With chronicity, there may be increased amounts of fibrosis and scarring at ulcer edges

## ANCILLARY TESTS

### Histochemistry

- Gram stain
  - Causative organisms can usually be identified
  - Usually gram-positive cocci
    - *Streptococcus pyogenes*

- Chains of organisms as seen in culture Gram stain may not be evident with tissue sections

### Microbiology

- Wound or tissue cultures
  - Gold standard for bacterial species identification
  - Cultures are often used to define antibiotic susceptibility for causative organisms

## DIFFERENTIAL DIAGNOSIS

### Histopathological

- Stasis ulceration
  - Does not respond to antibiotic treatment
  - Usually seen in older adults, not children
  - Stasis-related vascular proliferation in uninvolved superficial dermis
  - Hemosiderin is usually prominent
  - Edge of ulceration is not as abrupt and punched out
- Pyoderma gangrenosum
  - Does not respond to antibiotic treatment
  - Heavy neutrophil infiltrate with ulceration
  - Ulcer edges are thickened, clinically having rolled appearance
- Calciphylaxis
  - Does not respond to antibiotic treatment
  - Patients have history of significant chronic kidney disease or renal failure
  - Stellate ulcerations that are punched out
    - Usually intensely painful
  - Significant necrosis
  - May have dermal or subcutaneous calcifications
  - Inflammatory infiltrate is mixed
- Thrombosis-related ulceration
  - Does not respond to antibiotic treatment
  - Due to variety of thrombotic phenomena
  - Vessels will have thrombi
    - May be superficial or deeper vessels
    - Blood clot, fibrin, antibody mediated, foreign material, etc.

### Clinical

- Impetigo
  - Golden crust
  - Lesions are not punched out
  - Vesiculation occurs beneath stratum granulosum
  - Bacteria are identified with H&E &/or Gram stains
    - Responds to antibiotic treatment
  - Neutrophilic infiltrate in dermis and epidermis
    - May have acantholytic cells
- Trauma/prurigo
  - Does not respond to antibiotic treatment
  - Usually only 1 lesion, perhaps few
  - Not as widespread as ecthyma
  - Ulceration is not as punched out
  - Adjacent epidermis may have features of prurigo nodularis or lichen simplex chronicus

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# Erythrasma

## KEY FACTS

### TERMINOLOGY

- Erythematous intertriginous patches due to *Corynebacterium minutissimum* infection
  - Gram-positive bacillus

### CLINICAL ISSUES

- More frequently found in obese &/or diabetic patients
- More common in hot, humid environments
- Typical cases have well-defined erythematous patches in intertriginous areas, such as axilla and groin
- Nails may also be involved
  - Hyperkeratosis and onycholysis
- Coral-red fluorescence under Wood lamp examination
- Treatment
  - Antibiotics
    - Erythromycin is usual 1st-line drug
  - Topical therapies
    - Clindamycin, Whitfield ointment, sodium fusidate ointment, antibiotic soaps, bleach baths

### MICROSCOPIC

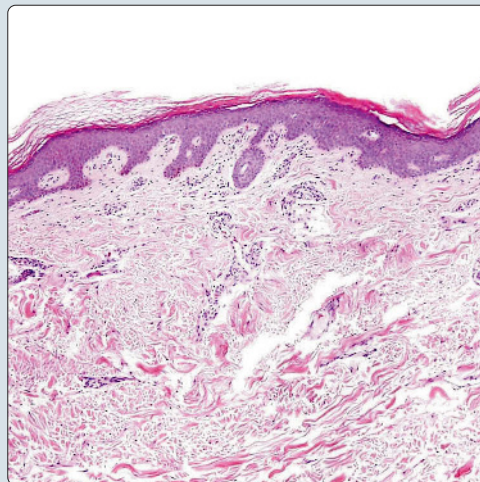
- Very few changes identified on routine hematoxylin and eosin staining
- May have hypergranulosis
- May have nonspecific superficial perivascular lymphocytic infiltrate
- Bacterial bacilli can usually be seen with careful examination of cornified layer on hematoxylin and eosin staining
  - Easier to identify with Gram stain

### TOP DIFFERENTIAL DIAGNOSES

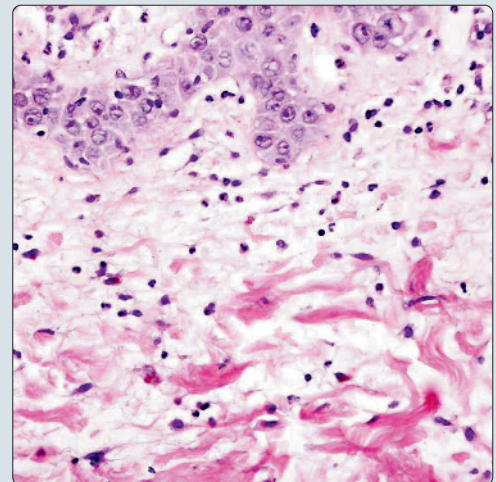
- Hailey-Hailey disease
- Acanthosis nigricans
- Psoriasis
- Intertrigo
- Dermatophytosis/candidiasis
- Viral exanthem

#### Minimal Inflammation

**(Left)** Despite the clinical appearance of an erythematous or hyperpigmented area in body creases, erythrasma usually has very sparse inflammation. **(Right)** Occasionally, neutrophils may also be a part of the dermal infiltrate. In this particular case, edema between the collagen fibers is also present.

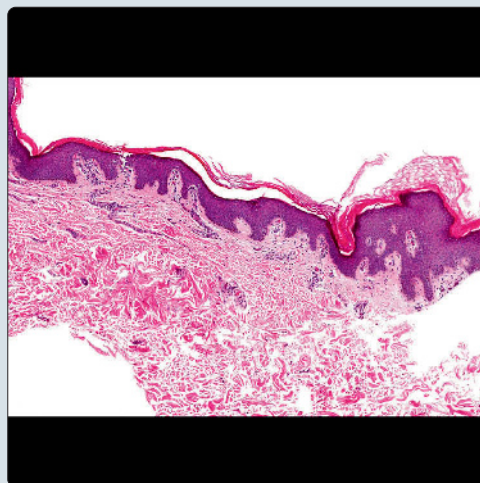


#### Neutrophils

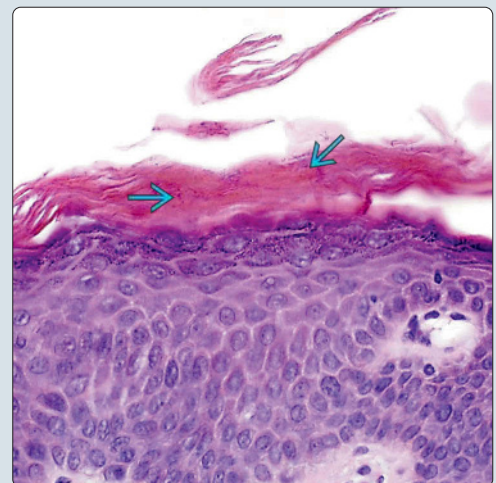


#### Hyperkeratosis and Acanthosis

**(Left)** Hyperkeratosis is usually seen. If the patient has been rubbing or scratching the affected area, acanthosis and hypergranulosis may also be a feature. Inflammation is still scant. **(Right)** Upon close inspection of the cornified layer, causative bacteria ➡ can be found in the areas of compact hyperkeratosis.



#### Bacteria in Cornified Layer





**TERMINOLOGY****Definitions**

- Erythematous intertriginous patches due to *Corynebacterium minutissimum* infection

**ETIOLOGY/PATHOGENESIS****Infectious Agents**

- *C. minutissimum*
  - Gram-positive bacillus

**CLINICAL ISSUES****Presentation**

- More frequently found in obese &/or diabetic patients
- More common in hot, humid environments
- Typical cases have well-defined erythematous patches in axilla and groin areas
  - Atypical cases may rarely present with nonintertriginous atrophic patches
  - Other intertriginous areas may be affected
    - Webbing of hands and toes
- Nails may also be involved
  - Hyperkeratosis
  - Onycholysis
- Typically not biopsied due to characteristic coral-red fluorescence under Wood lamp examination
  - Rare cases may not fluoresce
- Cases that are biopsied are usually due to lack of fluorescence or lack of Wood lamp to use during examination

**Treatment**

- Drugs
  - Antibiotics
    - Erythromycin is usual 1st-line drug
      - Others, such as clarithromycin, tetracycline, chloramphenicol, and others, may be efficacious
  - Topical therapies
    - Clindamycin
    - Whitfield ointment
    - Sodium fusidate ointment
    - Antibiotic soaps
    - Bleach baths

**Prognosis**

- Complete resolution with appropriate medical treatment

**MICROSCOPIC****Histologic Features**

- Very few changes identified on routine hematoxylin and eosin staining
  - Clinical history is critical
- May have hypergranulosis
- May have nonspecific superficial perivascular lymphocytic infiltrate
- Bacterial bacilli can usually be seen with careful examination of cornified layer on hematoxylin and eosin staining
  - Easier to identify with Gram stain

**ANCILLARY TESTS****Histochemistry**

- Gram stain
  - Identifies gram-positive bacilli in stratum corneum
- Periodic acid-Schiff (PAS) and Gomori methenamine silver (GMS)
  - Positive in fungal organisms, negative in erythrasma

**DIFFERENTIAL DIAGNOSIS****Histopathological**

- Viral exanthem
  - Minimal, if any, changes seen with hematoxylin and eosin staining
  - No bacteria in cornified layer
  - No fluorescence with Wood lamp
- Dermatophytosis/candidiasis
  - May have dermal inflammatory cell infiltrate composed of lymphocytes, neutrophils, &/or eosinophils
  - PAS &/or GMS identifies fungal elements in cornified layer

**Clinical**

- Hailey-Hailey disease
  - Bilateral, symmetrical, well-defined plaques in intertriginous areas
  - Skin may be cracked and weeping
  - No fluorescence with Wood lamp
  - Diffuse intraepidermal acantholysis
    - Dilapidated brick wall appearance on biopsy
- Acanthosis nigricans
  - Bilateral, symmetrical, velvety brown plaques in intertriginous areas
  - Common in patients with diabetes &/or obesity
  - No fluorescence with Wood lamp
  - Papillomatous epidermis with mild acanthosis and mild hyperkeratosis
- Psoriasis
  - Well-defined erythematous plaques with silver scale
  - No fluorescence with Wood lamp
  - Hyperkeratosis, hypogranulosis, and psoriasiform epidermal hyperplasia
  - Munro microabscesses in stratum corneum
  - Spongiform pustules of Kogoj in stratum spinulosum
  - Papillary dermal capillary dilatation
- Intertrigo
  - Nonspecific diagnosis referring to any intertriginous dermatosis
  - Typically due to infection with *Candida* species or *Staphylococcus aureus*

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## KEY FACTS

### TERMINOLOGY

- Unusual granulomatous response to bacterial infection, most commonly caused by *Escherichia coli*, *Staphylococcus aureus*, *Proteus*, *Mycobacterium tuberculosis*, *Klebsiella*

### ETIOLOGY/PATHOGENESIS

- Thought to be due to inability of macrophages to effectively phagocytize bacterial organisms in setting of immunosuppression &/or autoimmune disease

### CLINICAL ISSUES

- Usually occurs in genitourinary tract; however, can involve any internal organ or cutaneous surface
- On skin, lesions can present variably as papules, plaques, ulcers, and abscesses

### MICROSCOPIC

- Parakeratosis, pseudoepitheliomatous hyperplasia, and sheets of large macrophages in dermis admixed with lymphocytes, neutrophils, and plasma cells

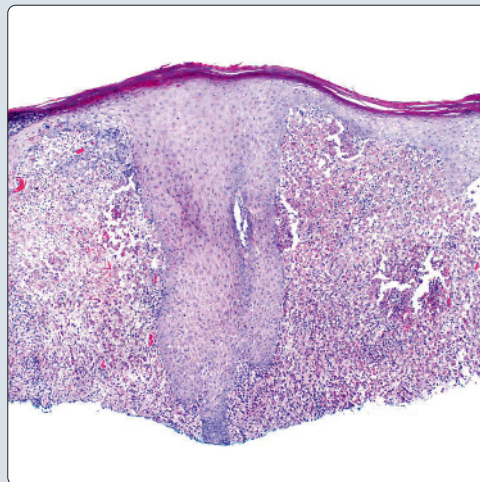
- Macrophages have abundant foamy cytoplasm and distinct, dark intracytoplasmic inclusions (Michaelis-Gutmann bodies), which represent partially ingested bacteria with calcification
- Von Kossa and PAS stains will highlight Michaelis-Gutmann bodies, helping to clinch right diagnosis

### TOP DIFFERENTIAL DIAGNOSES

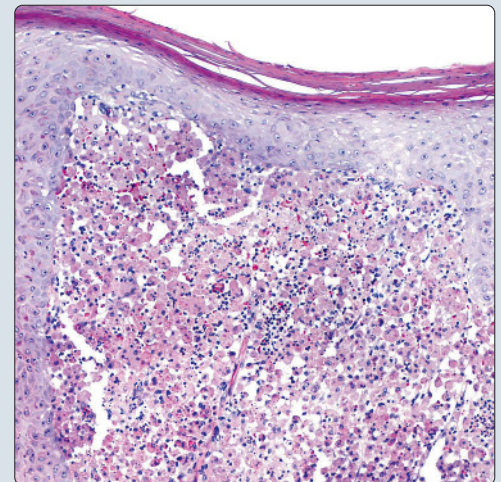
- Deep fungal or mycobacterial infections
- Xanthoma
- Langerhans cell histiocytosis
- Granular cell tumor

**Epithelial Hyperplasia With Sheets of Dermal Macrophages**

(Left) Sheets of large macrophages fill the dermis with overlying irregular epithelial hyperplasia and focal parakeratosis (original magnification x4). (Right) The characteristic large, round macrophages (von Hansemann cells) are admixed with neutrophils, lymphocytes, and plasma cells (original magnification x20).

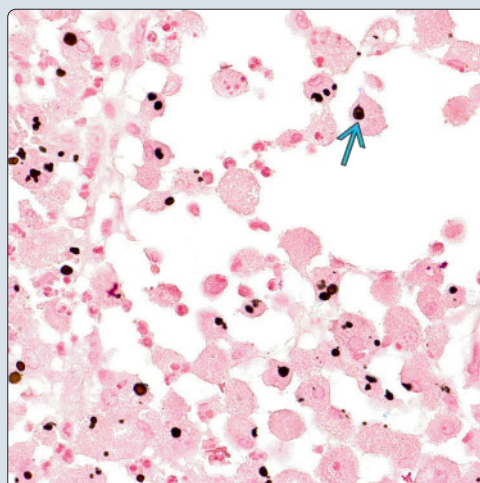


**Large Round Macrophages of Malakoplakia**

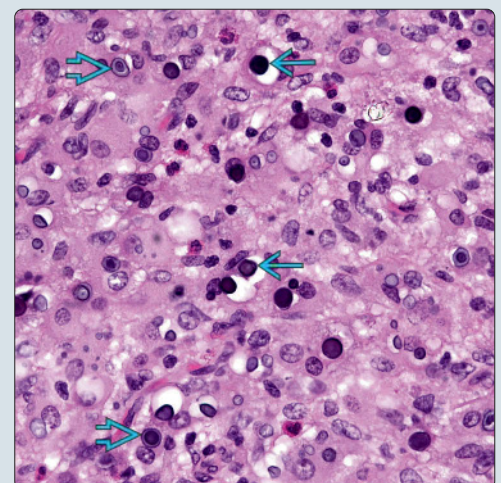


**Von Kossa Stain Highlighting Michaelis-Gutmann Bodies**

(Left) Michaelis-Gutmann bodies are highlighted by von Kossa stain (original magnification x40). (Right) This example of malakoplakia shows numerous Michaelis-Gutmann bodies within histiocytes, both targetoid and laminated. (From DP: Gastrointestinal, 2e.)



**Characteristic Malakoplakia With Michaelis-Gutmann Bodies**





## TERMINOLOGY

### Definitions

- Unusual granulomatous response to bacterial infection

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- Most common organisms include *Escherichia coli*, *Staphylococcus aureus*, *Proteus*, *Mycobacterium tuberculosis*, *Klebsiella*
- Thought to be due to inability of macrophages to effectively phagocytize bacterial organisms in setting of immunosuppression &/or autoimmune disease

## CLINICAL ISSUES

### Presentation

- Usually occurs in genitourinary tract; however, can involve any internal organ or cutaneous surface
- On skin, lesions can present variably as papules, plaques, ulcers and abscesses; there is no characteristic appearance

### Treatment

- Surgical excision ± systemic antibiotics
  - Antibiotics with good macrophagic penetration work well: Quinolones, trimethoprim/sulfamethoxazole
  - Clofazimine and penicillins have also been used with high cure rate
- Reduction or discontinuation of immunosuppressive medications should be considered if clinical setting allows

### Prognosis

- Prognosis for cutaneous malakoplakia is favorable with appropriate treatment as above; however, lesions may persist despite local and systemic therapy
- Morbidity and mortality primarily stem from underlying condition and involvement of visceral organs

## MICROSCOPIC

### Histologic Features

- Parakeratosis, pseudoepitheliomatous hyperplasia, and sheets of large macrophages in dermis admixed with lymphocytes, neutrophils, and plasma cells
- Macrophages have abundant foamy cytoplasm and distinct, dark intracytoplasmic inclusions (Michaelis-Gutmann bodies)
  - Represent partially ingested bacteria with calcification
- Von Kossa and PAS stains will highlight Michaelis-Gutmann bodies, helping to clinch right diagnosis

## DIFFERENTIAL DIAGNOSIS

### Deep Fungal or Mycobacterial Infections

- Pseudoepitheliomatous hyperplasia common; intraepithelial microabscesses
- Dense dermal mixed infiltrate; sometimes caseating granulomas (mycobacterial)
- PAS, GMS, AFB, and Fite stains, as well as tissue culture, can be helpful

### Xanthoma

- Pale staining foamy histiocytes with intracellular &/or extracellular lipid; no significant inflammation

### Langerhans Cell Histiocytosis

- Large cells with reniform (notched/kidney bean-like) nuclei; characteristic Birbeck granules (tennis racket-shaped) ultrastructurally
- Edema and eosinophils common
- S100 and CD1a positive

### Granular Cell Tumor

- Sometimes epidermal/pseudoepitheliomatous hyperplasia
- Large cells with small hyperchromatic nuclei, abundant eosinophilic granular cytoplasm, and indistinct cell borders
- Granules are S100, PAS, NKI-C3 positive

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Foamy histiocytes with distinct basophilic inclusions that are highlighted by von Kossa and PAS stains

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SECTION 20

# Spirochetal Diseases



Syphilis

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## KEY FACTS

### TERMINOLOGY

- Secondary syphilis (SS) occurs 4-8 weeks after primary chancre, usually as maculopapular, scaly patches or plaques characteristically involving palms and soles, extremities, trunk, and elsewhere

### MICROSCOPIC

- Lesions of SS have great histologic variability (considered "great simulator")
  - Can have psoriasiform hyperplasia, spongiosis, lichenoid, or perivascular infiltrate
  - Sometimes shows mixed pattern (lichenoid and psoriasiform are most common, also can be lichenoid and granulomatous)
- Perivascular lymphocytes are often mixed with plasma cells and sometimes neutrophils
- Infiltrates show greatest density in papillary dermis and diminish in reticular dermis

- Confirm diagnosis by identifying spirochetes on immunohistochemistry

### ANCILLARY TESTS

- Polyclonal antibody directed against *Treponema pallidum* is stain of choice for identifying organisms
  - Spirochetes mainly found within epidermis and upper dermis
- PCR can also be used on skin specimens, although not as sensitive as immunohistochemistry

### TOP DIFFERENTIAL DIAGNOSES

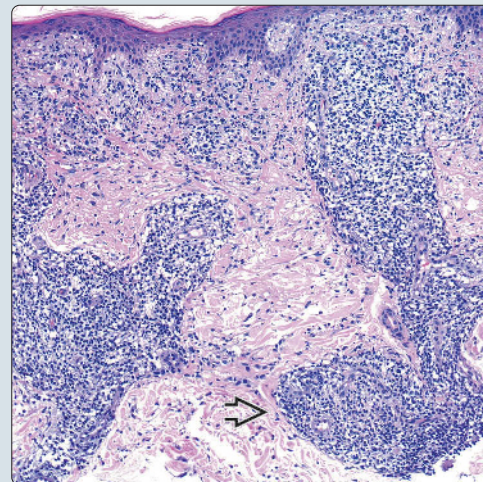
- Lichen planus
- Psoriasis
- Pityriasis lichenoides
- Psoriasiform drug reactions
- Lichenoid hypersensitivity reaction

**Widespread Maculopapular Rash of Secondary Syphilis**

(Left) This HIV-positive patient shows a widespread maculopapular eruption indicative of secondary syphilis (SS). (Courtesy G. Strauch, MD.) (Right) SS histologically shows interface changes with a dense perivascular lymphoplasmacytic dermal infiltrate ➡ that is greater in density in the papillary dermis and diminishes toward the base.

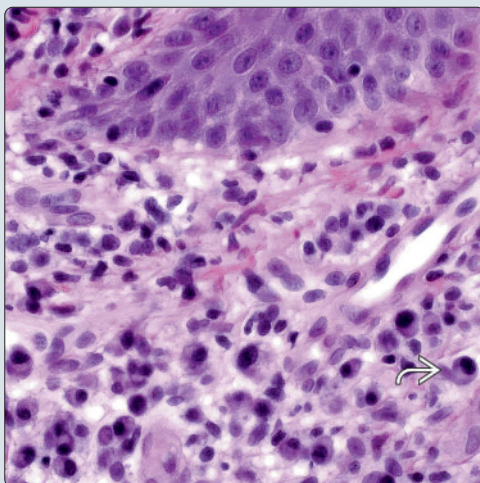


**Dense Lymphoplasmacytic Infiltrate**

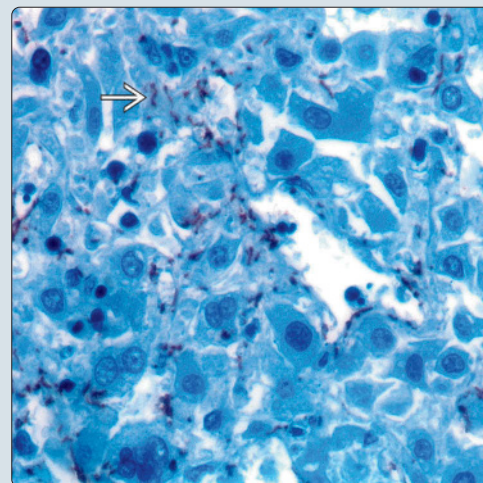


**Numerous Plasma Cells**

(Left) Lesions of SS histologically often contain numerous plasma cells ➡. (Right) Numerous spirochetes ➡ that are spiral-shaped are identified in this biopsy specimen using an immunohistochemical stain with a polyclonal antibody against *Treponema pallidum*.



**Spiral-Shaped Spirochetes on Immunohistochemistry**





## TERMINOLOGY

### Abbreviations

- Secondary syphilis (SS)

### Definitions

- Occurs 4-8 weeks after primary chancre, usually as maculopapular, scaly patches or plaques characteristically involving palms and soles, extremities, trunk

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- Results from hematogenous and lymphatic dissemination of *Treponema pallidum* and multiplication of microorganisms in different tissues
  - Occurs after untreated primary syphilis

## CLINICAL ISSUES

### Presentation

- Broad spectrum of clinical manifestations involving skin as well as other tissues
- Usually presents as maculopapular, scaly patches or plaques involving palms, soles, extremities, trunk
- Early (10%)
  - Generalized eruption, nonpruritic, roseola-like, discrete macules, initially distributed on flanks and shoulders
- Late (70%)
  - Generalized maculopapular and papulosquamous eruptions more infiltrated lesions, often copper colored
  - Annular polymorphic plaques on face, corymbose arrangement (satellite papules around larger central lesion), occurs in waves
- Localized syphilis (specific infiltrations of treponemes, positive dark-field examination)
  - Palms and soles: Symmetric papules and plaques with collarette of scale (collarette of Bielt)
  - Anogenital area: Condylomata lata resemble genital warts
  - Seborrheic area: "Corona veneris" along hairline
- Hypopigmented macules, mainly on neck (postinflammatory: "Necklace of Venus")

### Treatment

- Drugs
  - Parenteral penicillin is treatment of choice

## MICROSCOPIC

### Histologic Features

- Lesions of SS have great histologic variability (considered "great simulator")
  - Variable epithelial alterations
    - Can have psoriasiform hyperplasia, spongiosis, lichenoid, or perivascular infiltrate
    - Sometimes shows mixed pattern (lichenoid and psoriasiform are most common, also can be lichenoid and granulomatous)
  - Perivascular lymphocytes are often mixed with plasma cells and sometimes neutrophils
    - Intracorneal neutrophilic abscesses in some cases

- Infiltrates show greatest density in papillary dermis and diminish in reticular dermis
- Several histologic variants of SS exist
  - Condylomata lata (numerous treponemes)
    - More florid epithelial hyperplasia and intraepithelial microabscess enriched in neutrophils; silhouette is verrucous
  - Syphilitic alopecia
    - Superficial and deep perivascular and perifollicular lymphoplasmacytic infiltrate
    - Increased number of telogen hairs and sometimes concomitant necrotizing pustular folliculitis
  - Pustular lesions (rare)
    - Necrotizing pustular follicular reaction with noncaseating granulomata and perivascular lymphoplasmacytic infiltrate
    - Rupial syphilis: Strikingly thickened cornified layer with neutrophils and no granular cell layer
  - Syphilis cornée
    - Epidermal invagination containing horny plug composed of laminated layers of parakeratotic cells with loss of granular layer and thinning of stratum spinosum
  - Lues maligna (more common in HIV disease)
    - Ulcerative form with severe thrombotic endarteritis obliterans involving vessels at dermal-subcutaneous junction
    - Dense plasmacellular infiltrate with variable admixture of histiocytes may be observed

## ANCILLARY TESTS

### Immunohistochemistry

- Polyclonal antibody directed against *T. pallidum* is stain of choice for identifying organisms
- Spirochetes mainly found in epidermis and upper dermis

## DIFFERENTIAL DIAGNOSIS

### Lichen Planus

- Lichenoid interface dermatitis
- No spongiosis, deep inflammation or plasma cells

### Psoriasis

- Psoriasiform hyperplasia often with neutrophils in stratum corneum

### Pityriasis Lichenoides

- Pure lymphocytic middermal perivascular infiltrate, keratinocyte necrosis, and pronounced lymphocytic exocytosis

### Psoriasiform Drug Reactions

- Eosinophils and plasma cell infiltrate

### Lichenoid Hypersensitivity Reaction

- Usually eosinophils and plasma cells

## SELECTED REFERENCES

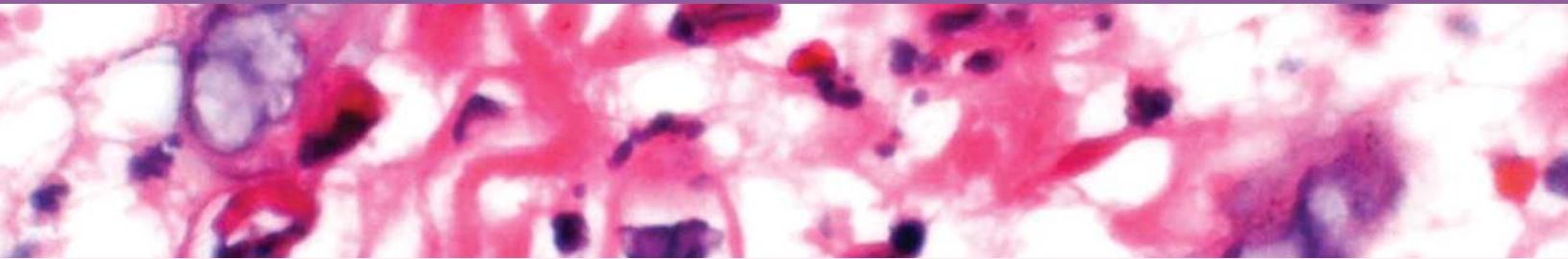
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## SECTION 21

# Viral Infections



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## Viral Exanthem

## KEY FACTS

## TERMINOLOGY

- Widespread rash that when due to viruses tends to affect children more than adults and can be associated with systemic symptoms, such as fever, headache, and malaise
- Importantly, viral exanthems can mimic morbilliform drug eruptions, which can also be widespread in nature but tend to affect adults more than children

## CLINICAL ISSUES

- Widespread pink macules and papules coalescing into plaques involving trunk and extremities
- Typically presents after prodrome as erythematous macules and papules, which tend to coalesce into plaques involving trunk &/or extremities

## MICROSCOPIC

- Varying degrees of epidermal change, spongiosis, and perivascular lymphocytic infiltrate

## TOP DIFFERENTIAL DIAGNOSES

- Drug eruption
  - Tends to have more eosinophils than viral exanthem
  - Tend to be are more morbilliform; tend to occur in older individuals
- Contact dermatitis
  - Increased intraepidermal Langerhans cells and presence of eosinophils are helpful
  - Very pruritic, usually elicited by history of exposure to inciting culprit
- Syphilis
  - Presence of plasma cells and spirochetes can aid in diagnosis
  - Can mimic any papulosquamous entity

Pink Papules of Pityriasis Rosea

(Left) This example shows pityriasis rosea (HHV-7) on the trunk of a 9-year-old boy. Note the horizontal orientation of the pink papules and plaques with minimal trailing scale. (Right) This is another example of pityriasis rosea (HHV-7) on the trunk of a 9-year-old boy. Note how the trailing scale lags behind the erythematous border of the papule, which is oriented horizontally along the Langer lines.

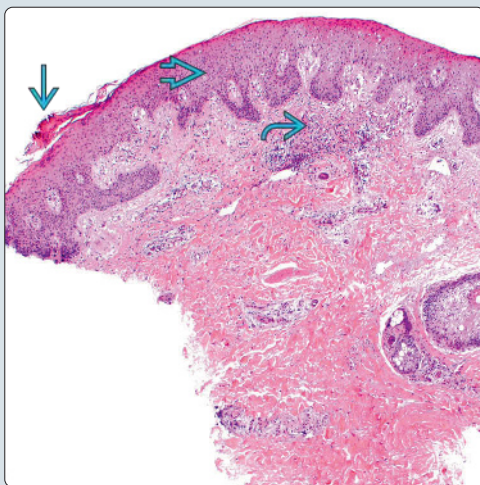


Trailing Scale of Pityriasis Rosea



Mounds of Parakeratosis in Pityriasis Rosea

(Left) Low-power H&E of pityriasis rosea shows mounding parakeratosis, acanthosis, and a mild superficial lymphocytic infiltrate. (Right) High-power view of pityriasis rosea shows mounding parakeratosis, acanthosis, focal spongiosis, a mild superficial lymphocytic infiltrate, and focal RBC extravasation.



Mounds of Parakeratosis and Focal Spongiosis





## TERMINOLOGY

### Synonyms

- Morbilliform-like rash, maculopapular rash

### Definitions

- Widespread rash that when due to viruses tends to affect children more than adults and can be associated with systemic symptoms, such as fever, headache, and malaise
- Importantly, viral exanthems can mimic morbilliform drug eruptions, which can also be widespread in nature but tend to affect adults more than children

## CLINICAL ISSUES

### Presentation

- Typically presents after prodrome as erythematous macules and papules, which tend to coalesce into plaques involving the trunk &/or extremities
- 1st disease (measles, a.k.a. rubeola): Due to paramyxovirus in unvaccinated children
  - Skin: Macules, papules spreading in cephalocaudal progression
  - Oral: Grayish papules (Koplik spots)
  - Prodrome common, complications can seriously affect brain, ears, lungs
- 2nd disease (scarlet fever): Due to group A, B hemolytic streptococci in young children
  - Skin: Sand paper-like, pink papules on neck, trunk, axilla (Pastia lines = petechial streaks in folds)
  - Oral: Strawberry red tongue
  - Fever, sore throat; complications can be rheumatic fever, EN, glomerulonephritis
- 3rd disease (German measles, a.k.a. rubella): Due to togavirus in unvaccinated children
  - Skin: 1st postauricular lymphadenopathy followed by papules on face, which spread acraly
  - Oral: (Forchheimer spots = red spots on soft palate)
  - Fewer systemic symptoms and clears within few days, unvaccinated children
- 5th disease (erythema infectiosum): Due to parvovirus B19
  - Skin: Slapped cheek appearance with bright red erythema on cheeks, lacy eruption on extremities
  - Few symptoms, but anemia can occur as well as miscarriage
- 6th disease (exanthem subitum, a.k.a. roseola): Due to herpes 6
  - Skin: After high fever resolves, elliptical rose red macules appear on trunk with white halos
  - Fever is sudden in onset, can result in seizures
- HHV-7: Often considered cause of pityriasis rosea
  - Skin: Herald patch, oval papules with trailing scale oriented along Langer lines on trunk, little on extremities, tends to occur after viral illness in spring time, spontaneously resolves
- HHV-8: Occurs mainly in HIV(+) as Kaposi sarcoma, multicentric Castleman disease, or primary effusion lymphoma
- Papular acrodermatitis of childhood (Gianotti-Crosti syndrome): Due to hepatitis B, EBV, Coxsackie
  - Skin: Sparing trunk, appears as papules and vesicles on extremities

- Infectious mononucleosis: Lymphadenopathy, fever, hepatosplenomegaly, morbilliform-like
- Varicella (chickenpox): Due to varicella zoster virus
  - Skin: Dew drops on rose petals starts on face, moves through trunk to extremities, extremely pruritic, crusts over; adults can get lethal pneumonia
- Unilaterothoracic exanthem: Can be bilateral but favors lateral trunk or axilla
- Papular purpuric gloves and socks syndrome: Due to parvovirus B19
  - Skin: Burning and pruritus of hands, feet with erythema, petechiae, self-limited

## MICROSCOPIC

### Histologic Features

- Epidermal features, spongiosis and perivascular lymphocytic infiltrate can vary from case to case

## ANCILLARY TESTS

### Serologic Testing

- Titers can be helpful in certain illnesses

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Drug eruptions: Tend to have more eosinophils than viral exanthem
- Contact dermatitis: Increased intraepidermal Langerhans cells and presence of eosinophils are helpful
- Syphilis: Presence of plasma cells and spirochetes can aid in diagnosis

### Clinical

- Drug eruptions: Tend to be more morbilliform; tend to occur in older individuals
- Contact dermatitis: Very pruritic, usually elicited by history of exposure to inciting culprit
- Syphilis: Can mimic any papulosquamous entity

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Widespread pink macules and papules coalescing into plaques involving trunk and extremities

### Pathologic Interpretation Pearls

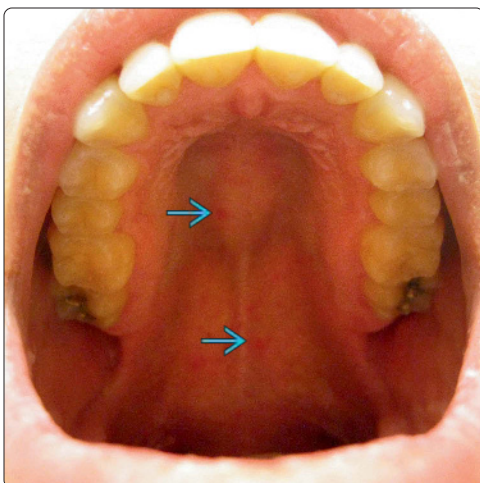
- Varying degrees of epidermal change, spongiosis, and perivascular lymphocytic infiltrate

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## Erosions on Hard Palate in Hand, Foot, and Mouth Disease

(Left) Patient with hand, foot, and mouth disease due to Coxsackie A16 virus, here with erosions of the hard palate, is shown. (Courtesy C. Yang, MD.) (Right) Patient with hand, foot, and mouth disease due to Coxsackie A16 virus, here with a pseudotargetoid erythematous macule on the plantar foot, is shown. Note the dusky center and erythematous border. (Courtesy C. Yang, MD.)

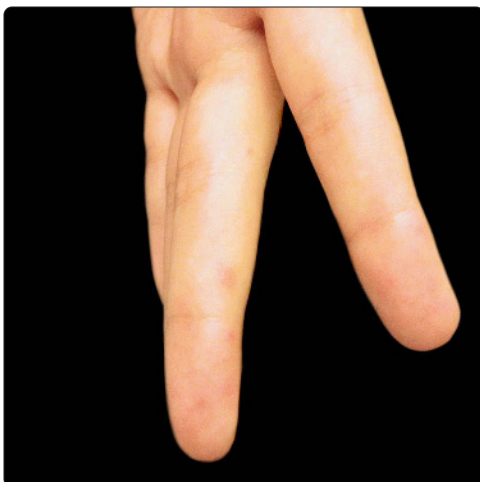


## Pseudotargetoid Macule in Hand, Foot, and Mouth Disease



## Pink Macules on Palmar Aspects of Digits

(Left) Patient with hand, foot, and mouth disease due to Coxsackie A16 virus, here with pink macules on the palmar aspects of the digits on the left hand, is shown. (Courtesy C. Yang, MD.) (Right) Low-power view shows what could be otherwise a normal biopsy with a sparse, barely visible, superficial perivascular lymphocytic infiltrate.

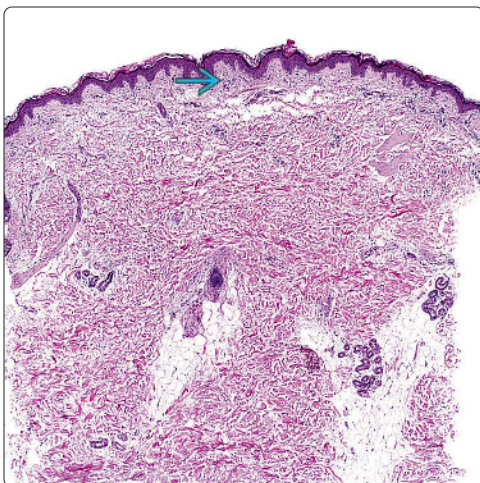


## Near Normal Appearance: Low Power

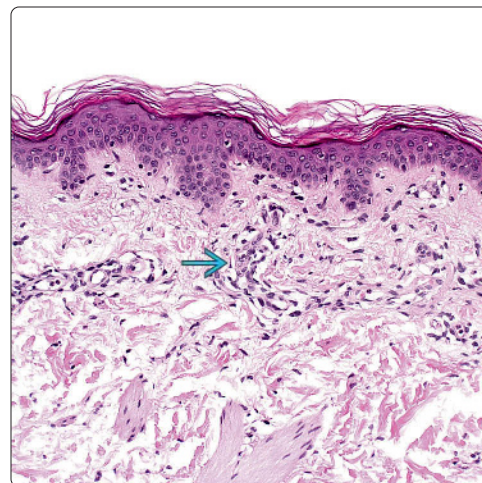


## Sparse Superficial Perivascular Infiltrate

(Left) Medium-power view shows what could be an otherwise normal biopsy with a sparse, barely visible, superficial perivascular lymphocytic infiltrate. (Right) Higher power view shows what could be an otherwise normal biopsy with a sparse, barely visible, superficial perivascular lymphocytic infiltrate.

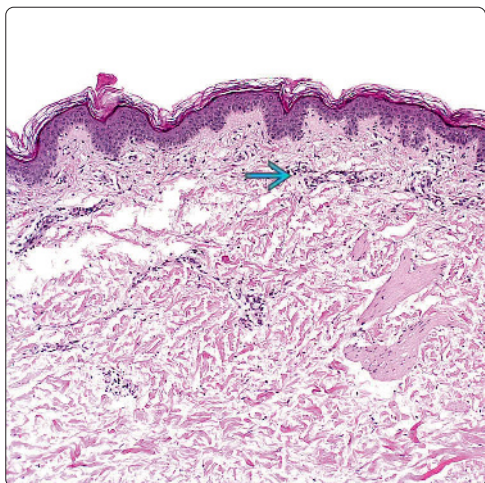


## Sparse Superficial Perivascular Infiltrate: Higher Power

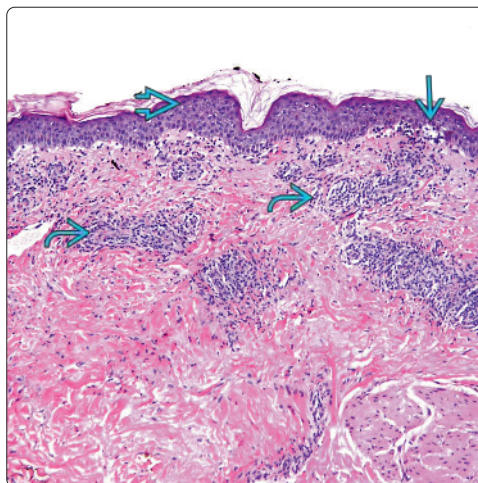




**Sparse, Superficial to Mid Deep Perivascular Infiltrate**

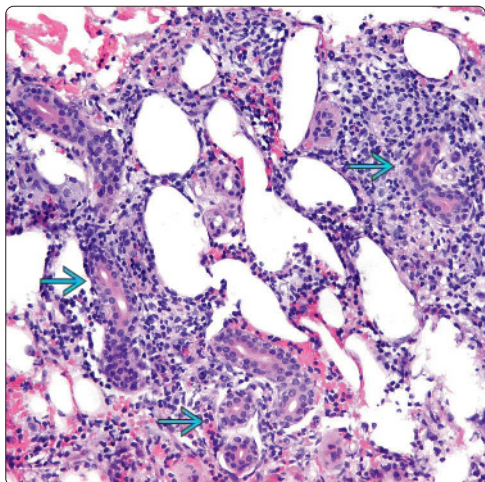


**Acanthosis, Spongiosis, and Superficial Perivascular Infiltrate**

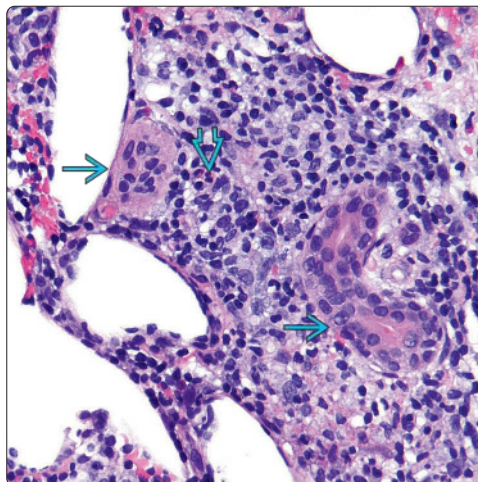


(Left) Medium-power view shows what could be an otherwise normal biopsy with a sparse, barely visible, superficial perivascular lymphocytic infiltrate. (Right) Viral exanthem, not otherwise specified, at medium power demonstrates mild acanthosis, spongiosis, and a superficial perivascular lymphocytic infiltrate. (Courtesy S. Wenson, MD.)

**Deep Dermal Lymphocytic Infiltrate**

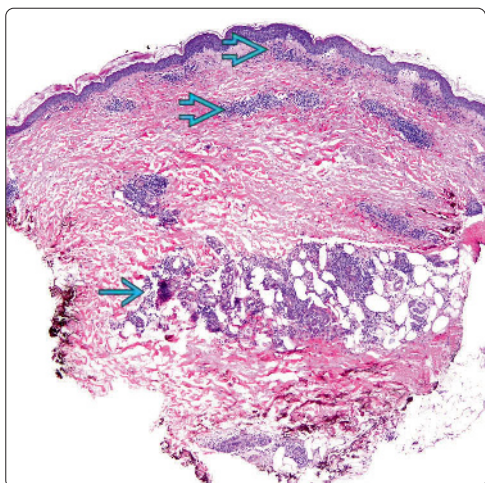


**Lymphocytic Infiltrate With Occasional Neutrophils**

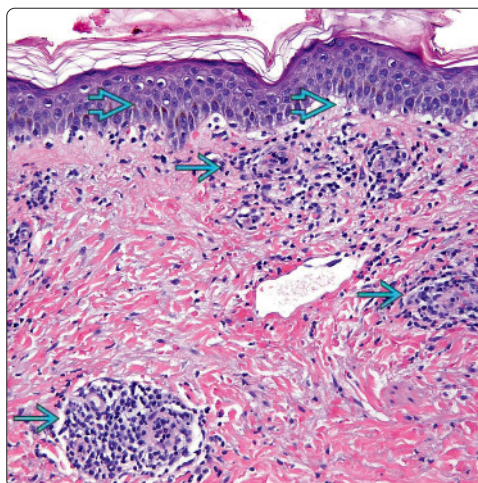


(Left) Viral exanthem, not otherwise specified, demonstrates a more intense presentation at high power with a deep dermal lymphocytic infiltrate involving the adnexal eccrine units. (Right) Viral exanthem, not otherwise specified, at higher power demonstrates a predominantly lymphocytic infiltrate involving the adnexal eccrine units. Occasional neutrophils can be seen, which is not uncommon in viral associated exanthems. (Courtesy S. Wenson MD.)

**Superficial and Deep Lymphocytic Infiltrate**



**Perivascular Lymphocytic Infiltrate With Spongiosis**



(Left) Viral exanthem, not otherwise specified, demonstrates a more intense presentation at low power with both a superficial perivascular lymphocytic infiltrate as well as a deep dermal lymphocytic infiltrate. (Right) Viral exanthem, not otherwise specified, demonstrates a more intense presentation at high power with a superficial perivascular lymphocytic infiltrate. Note the mild spongiosis. (Courtesy S. Wenson, MD.)



# Herpesvirus

## KEY FACTS

### TERMINOLOGY

- Infection by herpesvirus (HSV-1, HSV-2, and VZV)

### CLINICAL ISSUES

- Clear, fluid-filled vesicles that heal well, usually on mucosa sites (lip, eyes, genitals)
- For zoster, fever and malaise, then grouped vesicles in a dermatome distribution (area of skin supplied by same sensory ganglia)

### MICROSCOPIC

- Multinucleated keratinocytes with chromatin margination and molding
- Early lesion: Ballooning of keratinocytes with steel-gray nuclei and margination
- Late lesion: Necrotic keratinocytes with multinucleation and many neutrophils

### TOP DIFFERENTIAL DIAGNOSES

- Erythema multiforme

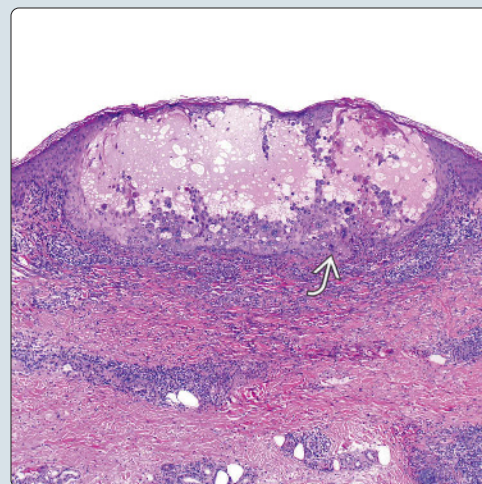
- Interface epidermal changes with necrotic keratinocytes
- No multinucleated cells with chromatin margination
- Hand, foot, and mouth disease
  - Intraepidermal vesicles with balloon cells and swelling of keratinocytes
  - No viral inclusions, no multinucleated cells
- Cytomegalovirus
  - Large nuclear inclusion
  - Enlarged, affected cells
  - Viral inclusion seen in endothelial cells, fibroblasts, and macrophages
- Orf (ecthyma contagiosum)
  - Eosinophilic cytoplasmic inclusion (not nuclear)
  - Clinically, larger lesions than herpetic whitlow
- Milker nodule
  - Both cytoplasmic and nuclear inclusions
  - Epidermal acanthosis with very elongated rete ridges
  - Multilocular vesicles

Grouped, Painful Vesicles on Upper Lip

(Left) *Herpes simplex* presents as grouped, painful vesicles on a red base on the upper lip. (Right) Low-power view of HSV infection demonstrates an intraepidermal vesicle with acantholysis and multinucleated and balloon cells with viral change evident from even this power. (Courtesy T. McCalmont, MD.)

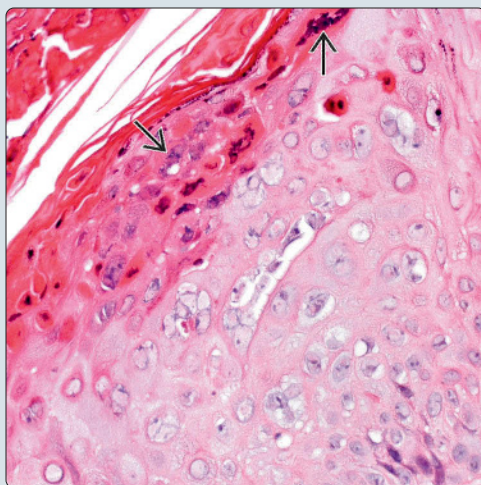


Intraepidermal Vesicle With Viral Cytopathic Changes

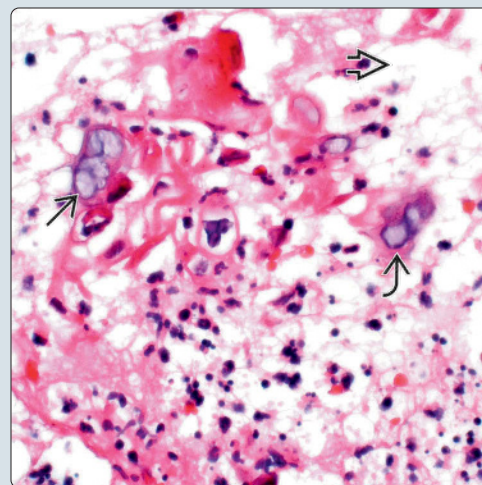


Multinucleation, Margination, and Molding

(Left) Early lesion of herpes shows multinucleation of the keratinocytes with margination and molding. (Right) Late lesion of herpes shows edema with neutrophils and debris along with diagnostic multinucleated keratinocytes with molding and margination.



Multinucleated Keratinocytes, Nuclear Molding, and Chromatin Margination





## TERMINOLOGY

### Synonyms

- Herpetic dermatitis
- Herpetic whitlow (hands)

### Definitions

- Infection by herpesvirus [HSV-1, HSV-2, and varicella zoster virus (VZV)]

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- Patients infected by fluids from infected person containing HSV-1 and HSV-2
- Enter mucosa or disrupted epidermis, then enter sensory ganglia and stay dormant or cause reinfection

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - 58% of USA population with HSV-1
  - ~ 17% of USA population with HSV-2
  - Higher for African Americans (39.2%) and higher for females (20.9%)
  - Very prevalent
    - HSV-1: 46-99% of population
    - HSV-2: 10-82% of population
- Age
  - Affects all ages
- Sex
  - Slightly more common in females
- Ethnicity
  - Higher for immigrants from developing countries

### Presentation

- Clear, fluid-filled vesicles that heal well, usually on mucosa sites (lip, eyes, genitals)
- For zoster, fever and malaise, then grouped vesicles in dermatome distribution (area of skin supplied by same sensory ganglia)
- Itchy and tingling sensation before vesicles
- For varicella, acute onset of vesicles at different stages throughout body

### Treatment

- Drugs
  - Acyclovir (guanosine analog that binds to viral DNA polymerase)

### Prognosis

- No cure but outbreaks are limited unless immunocompromised

## MICROSCOPIC

### Histologic Features

- Early lesion: Ballooning of keratinocytes with steel-gray nuclei and margination
- Rupture of blister with necrotic keratinocytes
- Ballooning degeneration of keratinocytes

- Keratinocytes with multinucleation, margination, and molding of nucleus
- Late lesion: Necrotic keratinocytes with multinucleation and many neutrophils

### Cytologic Features

- Tzanck smear: Margination of chromatin in multinucleated keratinocytes

## ANCILLARY TESTS

### Immunohistochemistry

- Specific antibodies to HSV-1, HSV-2, or VZV available

### Immunofluorescence

- Direct immunofluorescence for viral antigen

### In Situ Hybridization

- Probes for specific herpes genome to determine types of herpes infection

### PCR

- Amplify herpes DNA from fresh or formalin-fixed paraffin embedded tissue

### Serologic Testing

- Antibody titer to HSV can be determined by complement fixation reaction

## DIFFERENTIAL DIAGNOSIS

### Erythema Multiforme

- Interface epidermal changes with necrotic keratinocytes
- EM-like changes can be seen in herpes
- No multinucleated cells with chromatin margination
- Clinically, not grouped in 1 location

### Hand, Foot, and Mouth Disease

- Infection by picornavirus such as coxsackievirus A16
- Intraepidermal vesicles with balloon cells and swelling of keratinocytes
- No viral inclusions
- No multinucleated cells

### Cytomegalovirus

- Large nuclear inclusion
- Enlarged, affected cells
- Viral inclusion seen in endothelial cells, fibroblasts, and macrophages

### Orf (Ecthyma Contagiosum)

- Eosinophilic cytoplasmic inclusion (not nuclear)
- Caused by parapox virus
- Clinically, larger lesions than herpetic whitlow

### Milker Nodule

- Caused by paravaccinia virus
- Multilocular vesicles
- Epidermal acanthosis with very elongated rete ridges
- Both cytoplasmic and nuclear inclusions

## SELECTED REFERENCES

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## KEY FACTS

### TERMINOLOGY

- Varicella-zoster virus (VZV) causes primary varicella (chickenpox) in previously unexposed individuals and may later reactivate to cause herpes zoster (shingles)

### ETIOLOGY/PATHOGENESIS

- Primary varicella
  - Predominantly spread via airborne droplets
- Herpes zoster
  - Reactivation of VZV in dorsal root ganglion

### CLINICAL ISSUES

- Primary varicella
  - Pruritic, erythematous macules and papules starting on scalp and face, spreading cephalocaudally, then evolving into small vesicles with clear serous fluid surrounded by red halos
  - "Dew drops on rose petal"
- Herpes zoster

- Grouped vesicles on erythematous base develop within sensory dermatome; rarely cross midline

### MICROSCOPIC

- Intraepidermal blister with acantholytic keratinocytes in blister cavity
- 3 Ms: Multinucleation (multinucleated giant cells), molding of nuclei, and margination of chromatin
- Indistinguishable from herpes simplex virus (HSV) infection
- Verrucous variant
  - Prominent hyperkeratosis and epidermal acanthosis in addition to viral cytopathic changes

### TOP DIFFERENTIAL DIAGNOSES

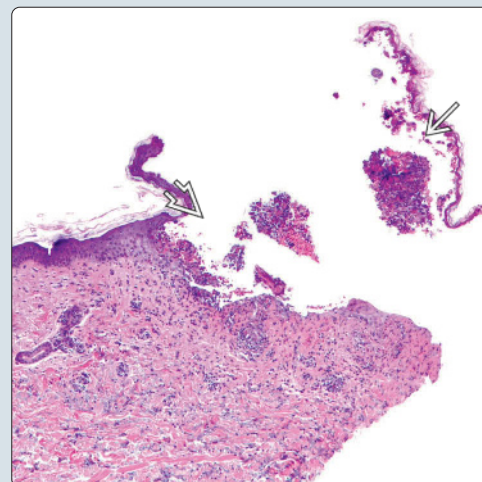
- Histopathologic
  - Indistinguishable from HSV infection
  - Coxsackie virus infection
  - Pemphigus vulgaris

Grouped Vesicles in V1 Distribution

(Left) An elderly patient with herpes zoster presented with grouped vesicles with hemorrhagic crusts over an erythematous base in the V1 distribution. (Right) At scanning magnification, intraepidermal blister and acantholytic cells are noted in this biopsy of primary varicella. (Courtesy H. Sidhu, MD.)

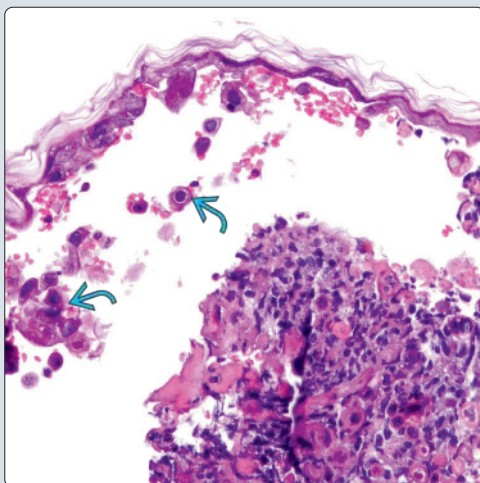


Intraepidermal Blister With Acantholytic Cells

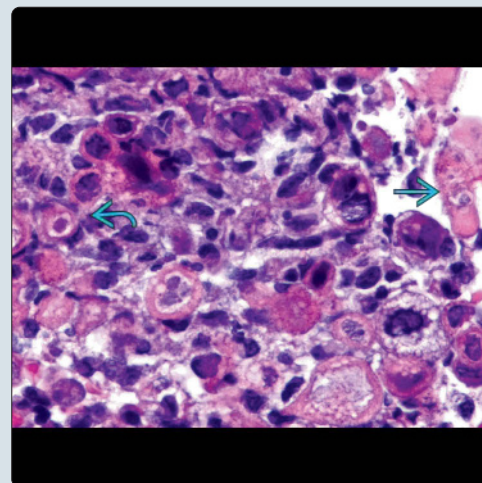


Acantholytic Cells With Viral Cytopathic Change

(Left) Within the intraepidermal blister cavity, acantholytic cells with viral cytopathic changes are seen. (Courtesy H. Sidhu, MD.) (Right) High-power view demonstrates Cowdry type A inclusions, which are small pink intranuclear inclusions surrounded by a clear halo. Nuclear molding as well as multinucleation are also evident in other cells in this biopsy specimen.



Cowdry Type A Inclusions





## TERMINOLOGY

### Abbreviations

- Varicella-zoster virus (VZV)

### Synonyms

- Varicella, chickenpox
- Herpes zoster, shingles

### Definitions

- VZV causes primary varicella (chickenpox) in previously unexposed individuals and may later reactivate to cause herpes zoster (shingles), especially in elderly and immunocompromised patients

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- VZV [human herpesvirus type 3 (HHV-3)]
  - Linear double-stranded DNA virus
- Primary varicella
  - Incubation period 10-21 days (average: 14-16 days)
  - Transmission via airborne droplets (viral replication in nasopharynx and conjunctiva) and, less frequently, skin-to-skin contact
  - Low-grade fever, malaise, and headaches usually present
  - Extremely contagious: 80-90% of susceptible household contacts developing clinical infection
  - Infectious for at least 4 days before and 5 days after appearance of exanthem
  - VZV travels to dorsal root ganglion cells, where it remains until reactivation at later date
- Herpes zoster
  - Caused by reactivation of VZV
    - Spontaneously or induced by stress, advancing age, or immunosuppression, leading to weakened cell-mediated immunity
  - Viral replication in dorsal root ganglion and sensory nerve causes painful neuralgia
  - Can give primary varicella to susceptible person via direct contact with vesicular fluid
    - Patients are no longer infectious once all lesions are crusted

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Primary varicella
    - Prior to universal vaccination, 3-4 million cases annually in USA
  - Herpes zoster
    - 10-20% lifetime chance of developing zoster for anyone with history of primary varicella
    - Risk of reactivation is higher if primary varicella infection was within 1st year of life
  - Risk of both varicella and herpes zoster increased in immunocompromised individuals (i.e., HIV)
- Age
  - Varicella
    - Now uncommon since advent of varicella vaccine; previously, 90% of children were affected by age 10

- Herpes zoster
  - Predominantly affects those older than 50 years of age

### Presentation

- Primary varicella
  - Prodrome of mild fever, malaise, myalgia
  - Pruritic, erythematous macules and papules starting on scalp and face, spreading cephalocaudally, then quickly evolving into small vesicles with clear serous fluid surrounded by red halos ("dew drops on rose petal")
  - Oral mucosa often involved
  - Lesions become pustular and crusted over 7-10 days; crops of lesions in different stages differentiate chickenpox from smallpox
- Herpes zoster
  - Rash often heralded by prodrome of pain, pruritus, tingling
  - Grouped vesicles on erythematous base develop within sensory dermatome; rarely cross midline

### Treatment

- Primary varicella
  - Antiviral treatment may not be necessary for healthy children
  - If started within 24-72 hours of onset of rash, acyclovir decreases duration and severity of disease
  - Symptomatic relief with antipyretics, antihistamines, calamine lotion, and tepid baths
  - In adults, antiviral treatment is indicated due to higher risk of more severe disease and complications (pneumonitis/hepatitis)
  - VZV immunoglobulins may be given as prophylaxis to immunocompromised patients and pregnant women for 1st-time exposure to VZV
- Herpes zoster
  - Antivirals most effective if started within 72 hours of onset of symptoms
  - Secondary vaccine for prevention of zoster available, approved for adults 60 years old and older
  - Prednisone &/or gabapentin may help decrease incidence of postherpetic neuralgia
  - Postherpetic neuralgia is treated with tricyclic antidepressants, gabapentin, or pregabalin
- Complications
  - Primary varicella
    - Most common complication: Secondary bacterial infection of lesions with resultant scarring
    - Rare CNS complications: Reye syndrome, encephalitis, acute cerebellar ataxia
    - Adults tend to have more severe symptomology; uncommonly, pneumonia may develop and has 10-30% mortality rate if untreated
    - Risk of congenital varicella highest during 1st trimester, with subsequent fetal abnormalities
  - Herpes zoster
    - Postherpetic neuralgia may develop in about 40% of patients > 60 years old (10% in those < 60)

### Prognosis

- In healthy children, disease runs benign, self-limited course

## MICROSCOPIC

### Histologic Features

- Indistinguishable from herpes simplex virus (HSV) infection
- Intraepidermal blister with acantholytic keratinocytes in blister cavity
- Balloon degeneration of keratinocytes with viral cytopathic changes, including
  - 3 Ms: Multinucleation (multinucleated giant cells), molding of nuclei, and margination of chromatin
  - Nuclear inclusions (called Cowdry type A inclusions): Small pink deposits with clear halo seen within nucleus
- Leukocytoclastic vasculitis more common in herpes zoster than varicella
- Verrucous variant
  - Prominent hyperkeratosis and epidermal acanthosis in addition to viral cytopathic changes

## ANCILLARY TESTS

### Immunofluorescence

- May be performed on cells scraped from base of freshly unroofed blister; differentiate between HSV-1, HSV-2, and VZV

### PCR

- May be used to differentiate between HSV-1, HSV-2, and VZV

### Culture

- Viral culture may be performed, but technically demanding with low sensitivity

### Tzanck Smear

- Quick and easy to perform; shows multinucleated giant cells common to HSV-1, HSV-2, and VZV

## DIFFERENTIAL DIAGNOSIS

### Histological

- HSV
  - Indistinguishable, need clinicopathological correlation, viral direct fluorescent antibody (DFA) or PCR to differentiate between viruses and to subtype
- Coxsackie virus infection (hand, foot, and mouth disease)
  - Intraepidermal vesiculation and acantholysis but no viral inclusions or multinucleated giant cells
- Pemphigus vulgaris
  - Clinical presentation distinct from varicella or zoster
  - Suprabasal clefting, a few acantholytic cells, no viral changes
  - However, patients with pemphigus vulgaris may have superimposed herpesvirus infection (Kaposi varicelliform eruption)
    - Special studies such as direct immunofluorescence may be helpful

### Clinical

- Varicella
  - Vesicular viral exanthem
    - ECHO, Coxsackie viruses
    - Negative Tzanck smear, HSV/VZV DFA or PCR testing
  - HSV

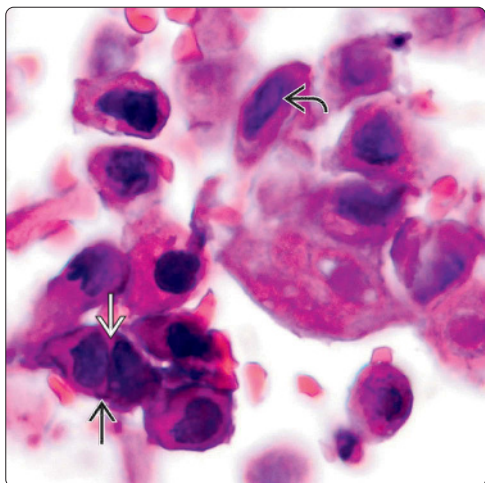
- Usually localized; however, may be disseminated
- May perform HSV/VZV DFA or PCR testing to differentiate
- Scabies (*Sarcoptes scabiei* mites)
  - Extremely pruritic papules favoring wrists, finger webs, periumbilicus, and genitals
  - Burrows may be seen on close visual inspection
- Pityriasis lichenoides et varioliformis acuta (PLEVA)
  - Chronic; some lesions with necrotic crust
- Rickettsial pox
  - History of exposure to mites
- Smallpox
  - Primarily historic concern, but threat of bioterrorism
  - More severe prodrome
  - Monomorphic lesions in same phase of development
  - Centrifugal spread
- Herpes zoster
  - Contact dermatitis
    - History of exposure to offending agent
    - Often pruritus rather than burning or pain
  - Bullous impetigo/cellulitis
    - Erythema, pain, warmth in affected area
    - May have serum leukocytosis and fever
  - Recurrent herpes simplex virus infection
    - Not dermatomal
    - Shingles serves as "booster," and most patients will have only single episode of zoster in lifetime
    - May be differentiated through viral DFA or PCR testing

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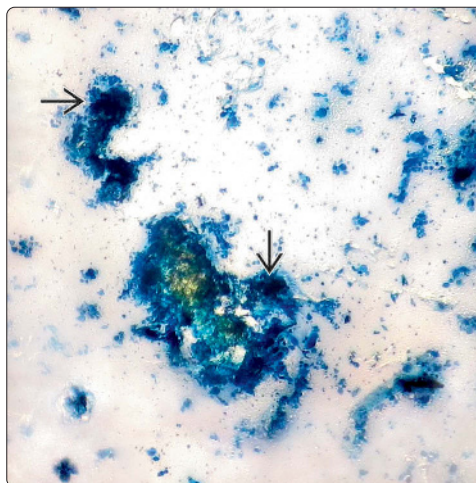
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## Multinucleation, Molding, and Margination of Chromatin



## Multinucleated Giant Cells



(Left) On higher power, multinucleation [box], molding [box], and margination [box] of chromatin are seen among the acantholytic cells. (Courtesy H. Sidhu, MD.) (Right) Tzanck smear shows multinucleated giant cells [box], which are characteristic of herpes simplex virus or varicella-zoster virus.

## "Dew Drop on a Rose Petal"

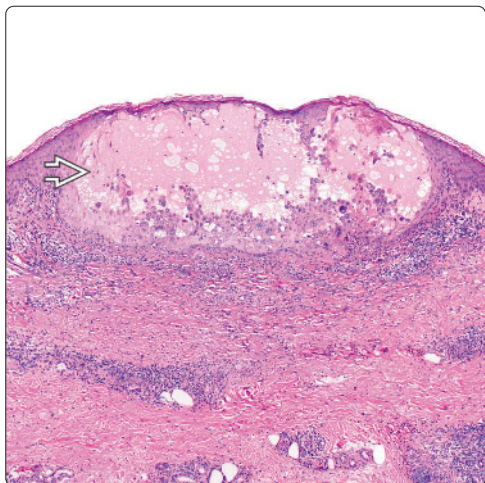


## Painful Grouped Vesicles

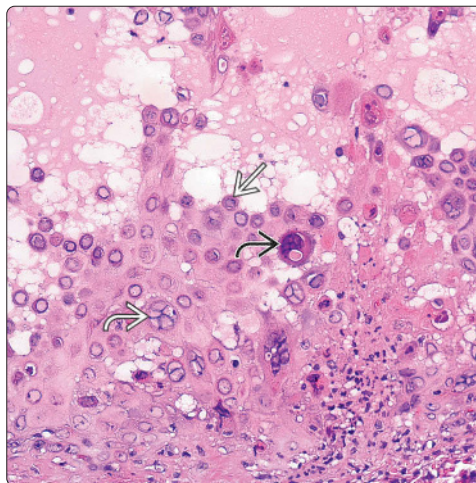


(Left) A small vesicle with clear fluid [box] on an erythematous base [box], a.k.a. "dew drop on a rose petal," is characteristic of varicella. (Courtesy A. Lipworth, MD.) (Right) Prior to developing painful grouped vesicles characteristic of shingles on his neck [box], this patient complained of burning and tingling in the area. (Courtesy A. Lipworth, MD.)

## Intraepidermal Blister of HSV



## Multinucleation, Molding, and Margination



(Left) HSV can appear indistinguishable with an intraepidermal blister [box] at low power. (Courtesy UCSF Dermatopathology Service.) (Right) High-power view of a case of HSV demonstrates multinucleation [box], nuclear molding [box], and margination of chromatin [box]. (Courtesy UCSF Dermatopathology Service.)



## KEY FACTS

### CLINICAL ISSUES

- Epstein-Barr virus (EBV) (human herpesvirus 4) is member of Herpesviridae family
  - Primarily transmitted through saliva
- EBV infection is responsible for many different diseases
- Infectious mononucleosis presents with triad of fever, pharyngitis, and lymphadenopathy
  - Copper-colored eruption is present in 80-100% of infectious mononucleosis patients who take ampicillin
- EBV is most common cause of Gianotti-Crosti in USA
- Gianotti-Crosti presents with pink, slightly pruritic, edematous, monomorphous papules or papulovesicles on cheeks, buttocks, extensor surfaces of extremities
- Oral hairy leukoplakia is found in immunocompromised patients and presents with corrugated, adherent, white plaques on lateral and dorsolateral surfaces of tongue

### MICROSCOPIC

- Infectious mononucleosis

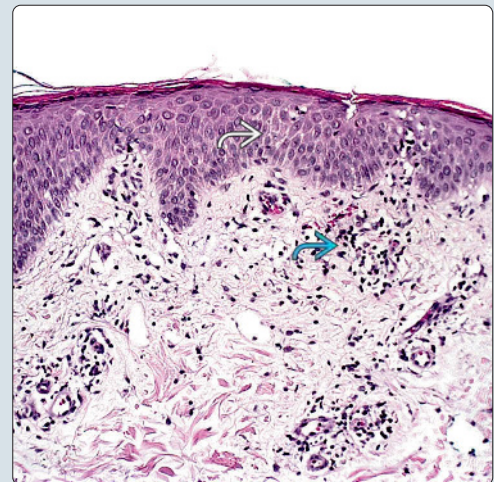
- Sparse, superficial, perivascular lymphocytic infiltrate, spongiosis, parakeratosis
- Ampicillin-induced eruption may have vacuolar interface pattern with denser inflammatory infiltrate with lymphocytes, neutrophils, eosinophils
- Gianotti-Crosti syndrome
  - Sparse, superficial, perivascular lymphocytic infiltrate, acanthosis, spongiosis, and focal lymphocytic exocytosis
  - Papillary dermal edema, extravasated erythrocytes, and endothelial swelling can often be seen
  - Vesicles containing lymphocytes and Langerhans cells may also be present
- Oral hairy leukoplakia
  - Irregular parakeratosis, acanthosis, and pale staining of epidermis (balloon change)
  - Ballooned cells have characteristic eosinophilic, ground-glass intranuclear inclusions with margination and beading of chromatin
  - Presence of EBV can be highlighted with ancillary studies

**Copper-Colored Macules With Confluence in Infectious Mononucleosis**

(Left) Ampicillin-induced eruption is shown in a patient with infectious mononucleosis due to Epstein-Barr virus (EBV) infection. Generalized copper-colored macules have become confluent. (Right) Infectious mononucleosis shows a sparse, superficial, perivascular, lymphocytic infiltrate, spongiosis, and parakeratosis similar to other viral exanthems.



**Superficial Perivascular Lymphocytic Infiltrate With Spongiosis**



**Pink Monomorphous Papules on Bilateral Extensor Surfaces**

(Left) Gianotti-Crosti syndrome presents as multiple pink monomorphous papules on the extensor surfaces of bilateral arms, hands, and legs. (Courtesy E. Newman, MD.) (Right) Gianotti-Crosti syndrome shows monomorphous edematous papules on the dorsal hand. (Courtesy E. Newman, MD.)



**Monomorphous Edematous Papules in Gianotti-Crosti Syndrome**





## TERMINOLOGY

### Abbreviations

- Epstein-Barr virus (EBV)

### Synonyms

- Human herpesvirus 4

### Definitions

- Member of Herpesviridae family
- Humans are only known reservoir for EBV
- DNA virus

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- Infects and can remain latent inside B cells by binding cell surface complement receptors CR2 or CD21
  - In immunocompetent patients, cell-mediated response toward EBV prevents immortalization of infected B cells
  - In immunocompromised patients, EBV-infected B cells may transform and give rise to EBV-induced lymphoproliferative disorders or neoplasms
- Also capable of infecting T cells, natural killer cells, smooth muscle, endothelial cells, macrophages, and monocytes
- Primarily transmitted through saliva

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - One of the most prevalent viruses, affecting 90-95% of world population
- Age
  - Infects both children and adults

### Presentation

- Responsible for variety of diseases
  - Infectious mononucleosis
    - Syndrome caused by primary infection with EBV
    - Occurs in children and young adults
    - Triad of fever, pharyngitis, and lymphadenopathy
    - Mucocutaneous findings include petechiae at junction of hard and soft palate, eyelid petechiae, and periorbital edema
    - Copper-colored macular rash present in 10-15% of infectious mononucleosis patients; if ampicillin (or less commonly, amoxicillin, penicillin, or cephalosporin) is administered, percentage increases to 80-100%
    - Other associated findings include headache, malaise, fatigue, hepatosplenomegaly, and lymphocytosis
  - Gianotti-Crosti syndrome
    - a.k.a. papular acrodermatitis of childhood
    - EBV is most common cause in United States
    - Other causes include other viral infections, bacterial infections, and immunizations
    - Cutaneous findings are pink, slightly pruritic, edematous, monomorphous papules or papulovesicles on cheeks, buttocks, and extensor surfaces of extremities
    - Positive Koebner phenomenon
    - Associated findings include fever, lymphadenopathy, and upper respiratory symptoms

- Oral hairy leukoplakia
  - Most commonly found in immunocompromised patients (HIV, post transplant, chemotherapy)
  - Mucosal findings are corrugated, adherent, white plaques on lateral and dorsolateral surfaces of tongue
- Other EBV-associated diseases include
  - Nasopharyngeal carcinoma
  - Posttransplant lymphoproliferative disorder
  - Burkitt lymphoma
  - Hodgkin lymphoma
  - Extranodal NK/T-cell lymphoma
  - Kikuchi histiocytic necrotizing lymphadenitis
  - Angioimmunoblastic T-cell lymphoma
  - Peripheral T-cell lymphoma
  - Midline destructive disease, midline lethal granuloma
  - Lymphomatoid granulomatosis
  - Hypersensitivity to mosquito bites
  - Hydroa vacciniforme
  - Pityriasis lichenoides
  - Lipschütz ulcer
  - Erythema nodosum
  - Erythema annulare centrifugum
  - Erythema multiforme

### Laboratory Tests

- Heterophile antibody test (monospot test)
- EBV serology
- EBV polymerase chain reaction
- Lymphocytosis
- Abnormal liver function tests

### Treatment

- Varies according to disease
  - Infectious mononucleosis
    - Majority of cases are self-limited
    - Supportive care
  - Gianotti-Crosti syndrome
    - Majority of cases are self-limited
    - Antihistamines to alleviate pruritus
    - Midpotency topical steroids
    - Systemic corticosteroids reserved for severe cases
  - Oral hairy leukoplakia
    - Topical podophyllin, topical retinoids, gentian violet
    - Cryotherapy
    - Surgical excision
    - Oral antiviral medication (acyclovir, valacyclovir, ganciclovir)

### Prognosis

- In immunocompetent patients, many diseases caused by EBV are self-limited
- In immunocompromised patients, EBV infection may give rise to life-threatening malignancies

## MICROSCOPIC

### Histologic Features

- Infectious mononucleosis
  - Nonspecific: Similar to other viral exanthems
  - Sparse, superficial, perivascular lymphocytic infiltrate, spongiosis, parakeratosis

- Ampicillin-induced eruption may have vacuolar interface pattern with denser inflammatory infiltrate with lymphocytes, neutrophils, eosinophils
- Gianotti-Crosti syndrome
  - Sparse, superficial, perivascular lymphocytic infiltrate, acanthosis, spongiosis, and focal lymphocytic exocytosis
  - Papillary dermal edema, extravasated erythrocytes, and endothelial swelling can often be seen
  - Vesicles containing lymphocytes and Langerhans cells may also be present
- Oral hairy leukoplakia
  - Irregular parakeratosis, acanthosis, and pale staining of epidermis (balloon change)
  - These ballooned cells have characteristic eosinophilic, ground-glass intranuclear inclusions with margination and beading of chromatin
  - Presence of EBV can be highlighted with immunohistochemical stains, in situ hybridization, or polymerase chain reaction

## ANCILLARY TESTS

### In Situ Hybridization

- EBV-encoded RNA chromogenic in situ hybridization highlights presence of EBV

## DIFFERENTIAL DIAGNOSIS

### Infectious Mononucleosis

- Other viral exanthems
  - Sparse, superficial, perivascular and interstitial lymphocytic infiltrate, spongiosis, and parakeratosis
  - May have vacuolar interface dermatitis, necrotic keratinocytes, and papillary dermal edema
- Drug eruption
  - Sparse, superficial, perivascular and interstitial infiltrate of lymphocytes and eosinophils, spongiosis, and parakeratosis
  - May have vacuolar interface dermatitis and necrotic keratinocytes
- Cytomegalovirus
  - Similar superficial perivascular infiltrate as other viral exanthems
  - Characteristic owl's eye viral inclusion body in cytoplasm and nuclei of endothelial cells
- Toxoplasmosis
  - Sparse, superficial, perivascular and interstitial lymphocytic infiltrate
  - Definitive diagnosis requires identification of tachyzoites, pseudocysts, or cysts in other tissues (brain, lung, bone marrow)

### Gianotti-Crosti Syndrome

- Arthropod assault
  - Superficial and deep infiltrate consisting of lymphocytes, eosinophils, and neutrophils
  - Spongiosis, intraepidermal vesicles, and papillary dermal edema may be present
- Allergic contact dermatitis
  - Spongiosis, superficial perivascular infiltrate with occasional eosinophils may be present

- Spongiosis, intraepidermal vesicles, and papillary dermal edema may be present
- Drug reaction
  - Sparse superficial perivascular and interstitial infiltrate of lymphocytes and eosinophils, spongiosis, and parakeratosis

### Oral Hairy Leukoplakia

- Leukoedema
  - Ballooned cells with pyknotic nuclei, but no inclusion bodies or chromatin beading
  - Present on buccal mucosa
- Chronic bite injury
  - Balloon change due to edema not viral cytopathic effect
  - Unlike oral hairy leukoplakia, has fissures and clefts lined by bacteria
- White sponge nevus
  - Hyperkeratosis, acanthosis, but no inclusion bodies or chromatin beading
  - Commonly found on buccal mucosa but can be found on ventral tongue

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

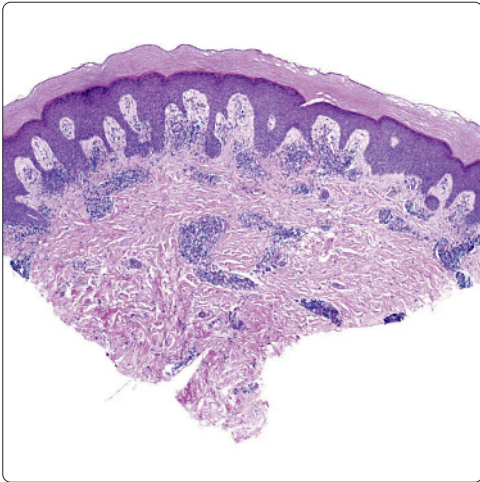
- Infectious mononucleosis
  - Similar to other viral exanthems
  - Sparse, superficial, perivascular, lymphocytic infiltrate; spongiosis; parakeratosis
- Gianotti-Crosti syndrome
  - Sparse superficial perivascular lymphocytic infiltrate, acanthosis, spongiosis, focal lymphocytic exocytosis, and papillary dermal edema
- Oral hairy leukoplakia
  - Irregular parakeratosis, acanthosis, and pale staining of epidermis (balloon change) with characteristic eosinophilic, ground-glass intranuclear inclusions with margination and beading of chromatin

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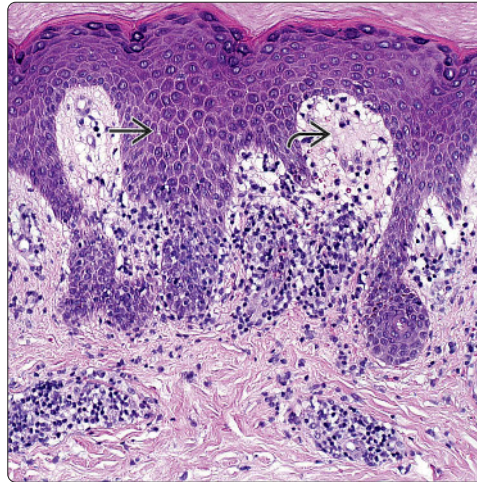
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**Superficial Perivascular Infiltrate With Papillary Dermal Edema**



**Spongiosis, Acanthosis, Edema, and Perivascular Lymphocytic Infiltrate**

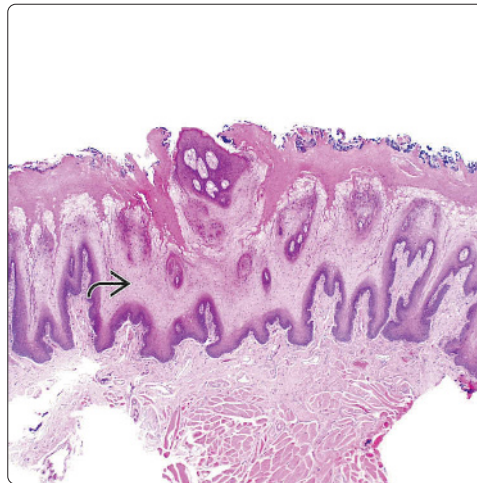


(Left) Gianotti-Crosti syndrome shows superficial perivascular inflammation and papillary dermal edema. (Right) Gianotti-Crosti syndrome shows spongiosis [box], acanthosis, and focal lymphocyte exocytosis with papillary dermal edema [box], superficial perivascular lymphocytic infiltrate, and extravasated erythrocytes.

**White Adherent Corrugated Plaque of Oral Hairy Leukoplakia**

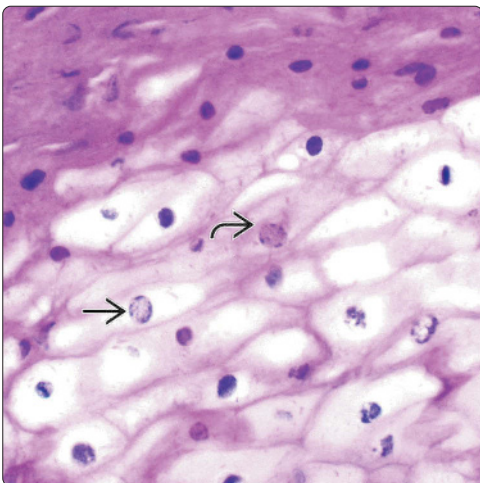


**Irregular Parakeratosis, Acanthosis, and Pale Epidermal Staining**

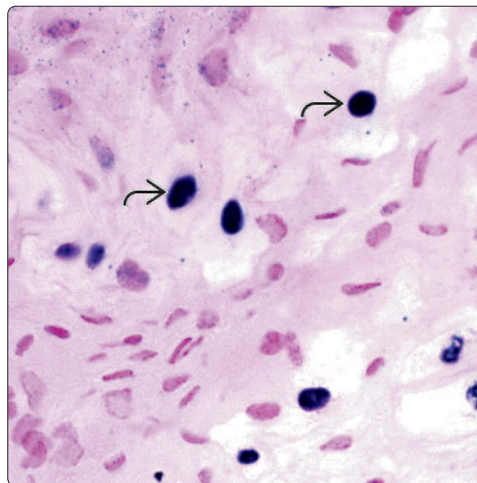


(Left) Oral hairy leukoplakia presents with white, adherent, corrugated plaque [box] on the lateral surface of the tongue. (Courtesy J. Wright, DDS, MS.) (Right) Oral hairy leukoplakia shows characteristic features of irregular parakeratosis, acanthosis, and pale staining [box] of the epidermis. (Courtesy J. Wright, DDS, MS.)

**Ground-Glass Intranuclear Inclusions of Oral Hairy Leukoplakia**



**EBV-Encoded RNA In Situ Hybridization Positivity in Oral Hairy Leukoplakia**



(Left) Oral hairy leukoplakia histologically shows balloon change of epidermal keratinocytes with characteristic ground-glass intranuclear inclusions [box] with margination and beading [box] of the chromatin. (Courtesy J. Wright, DDS, MS.) (Right) Oral hairy leukoplakia with Epstein-Barr-encoded RNA chromogenic in situ hybridization highlights the presence of EBV [box]. (Courtesy J. Wright, DDS, MS.)



## KEY FACTS

### TERMINOLOGY

- Viral infection due to cytomegalovirus (CMV), member of Herpesviridae family

### CLINICAL ISSUES

- Majority are asymptomatic, latent, lifelong infections
- Patients with clinical signs/symptoms are primarily immunosuppressed individuals
- Skin manifestations are uncommon and nonspecific
  - Maculopapular rash, ulcers, urticaria, blistering eruptions, epidermolytic and keratotic lesions
- Immunocompromised patients present with pneumonia, retinitis, and gastrointestinal disease
- 50-80% of USA population exposed to CMV by age 40
- Infects 1-4% of pregnant women in USA
  - Congenital CMV infection
    - "Blueberry muffin baby"
    - Generalized purple-blue macules, patches, papules, and nodules due to extramedullary hematopoiesis


### MICROSCOPIC

- Nonspecific infiltrate in dermis with dilated dermal vessels
- Endothelial cells are enlarged (i.e., cytomegaly)
  - Large eosinophilic or basophilic intranuclear inclusions with halo
  - "Owl's eye" nucleus
- $\pm$  hemorrhage

### ANCILLARY TESTS

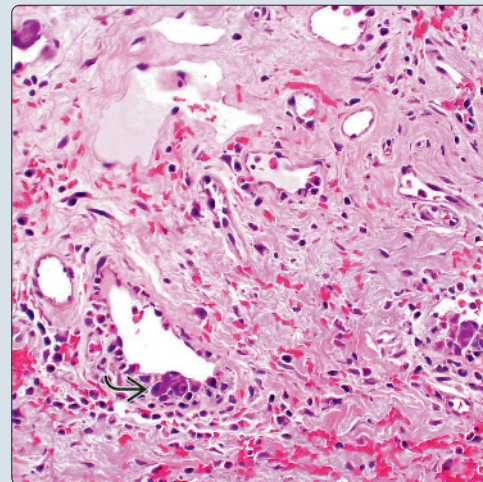
- Immunohistochemistry
  - Monoclonal antibody to CMV is commercially available
- PCR
  - Available on affected tissue and formalin-fixed, paraffin-embedded specimens
- Serology
  - Can confirm history of infection

**Punched-Out Ulcers**



**(Left)** Cytomegalovirus (CMV) infection shows punched-out ulcers with surrounding erythema and purulent exudate in the intergluteal cleft. **(Right)** CMV infection shows swollen, irregular endothelial cells with viral cytopathic changes and intranuclear purple inclusions  that don't always resemble an "owl's eye." (Courtesy J. Wright, DDS.)

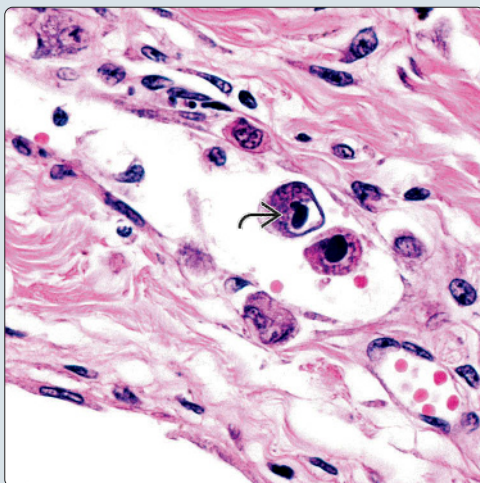


**Plump Endothelial Cells**

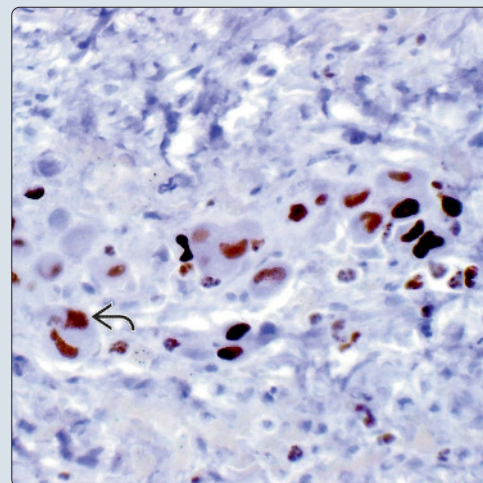


**Large Intranuclear Inclusions**

**(Left)** CMV infection shows dilated blood vessels with large protruding endothelial cells with basophilic intranuclear viral inclusions  and peripheral halo that resemble "owl's eyes." **(Right)** Immunohistochemistry using a monoclonal antibody against CMV shows brown viral nuclear inclusions . (Courtesy J. Wright, DDS.)



**Positive Immunostaining**





## TERMINOLOGY

### Abbreviations

- Cytomegalovirus (CMV)

### Definitions

- Viral infection due to CMV, member of Herpesviridae family

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- CMV

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - 50-80% of USA population exposed to CMV by age 40
  - Higher in developing countries and in areas with lower socioeconomic status
  - Immunocompromised and renal failure patients have most clinical symptoms
  - Infects 1-4% of pregnant women in USA
    - Congenital CMV infection in 1/3 of cases

### Presentation

- Majority are asymptomatic, latent, lifelong infection
  - Minority initially have mononucleosis-like syndrome
    - Fever and mild hepatitis
- Immunocompromised patients present with pneumonia, retinitis, and gastrointestinal disease
- Skin manifestations are uncommon and nonspecific
  - Maculopapular rash, ulcers, urticaria, blistering eruptions, epidermolytic and keratotic lesions
- Congenital CMV infection
  - "Blueberry muffin baby"
    - Generalized purple-blue macules, patches, papules, and nodules due to extramedullary hematopoiesis

### Treatment

- Antivirals (ganciclovir, valganciclovir, foscarnet) in immunocompromised individuals with retinitis or life-threatening infection

### Prognosis

- Excellent in healthy individuals
- May be life threatening in immunosuppressed individuals
- Disabilities in babies affected with congenital infection may be permanent

## MICROSCOPIC

### Histologic Features

- Nonspecific infiltrate in dermis with dilated dermal vessels
- Endothelial cells are enlarged (i.e., cytomegaly)
  - Large eosinophilic, amphophilic, or basophilic intranuclear inclusions
    - May be surrounded by halo
    - Resemble "owl's eye"
- Occasionally, features of leukocytoclastic vasculitis may be apparent
- ± hemorrhage

## ANCILLARY TESTS

### Immunohistochemistry

- Monoclonal antibody to CMV is commercially available

### PCR

- Available on affected tissue and formalin-fixed, paraffin-embedded specimens

### Serologic Testing

- Can confirm history of infection

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Angiosarcoma
  - Nuclear atypia may resemble CMV inclusions
  - Interanastomosing irregular vascular channels
  - Mitoses
  - Poorly circumscribed
- Atypical vascular lesion
  - Lesion of breast after surgery or radiation therapy
  - Increased numbers of irregular vascular channels
  - Hobnailed endothelial cells without atypia
  - Fairly well circumscribed

### Clinical

- Herpes simplex virus type 1 or 2
  - Nuclear inclusions
    - Glassy, gray nuclear inclusions with chromatin margination
    - Multinucleation
- Urticaria
  - Interstitial neutrophils and eosinophils
  - Superficial dermal edema
  - No vascular changes
- Blistering disorders
  - Vesicles or bullae present
  - Immunofluorescence may have characteristic staining patterns

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Look for endothelial cells resembling "owl's eye"
  - Keep in mind that all infected cells may not have such characteristic appearance
- There is higher chance of finding characteristic changes of CMV infection in ulcers compared with other skin lesions
- When in doubt, use immunohistochemistry or PCR to detect CMV

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## Orf and Milker's Nodule

## KEY FACTS

## TERMINOLOGY

- Clinically and histologically similar entities caused by infection with *Parapoxvirus* variants from occupational exposure to farm animals, presenting as red-blue papules that later crust and resolve spontaneously

## CLINICAL ISSUES

- Most commonly on forearm or hand; less common on face and perianal regions via autoinoculation
- Eruption of well-circumscribed, red-blue papule(s) measuring 1-2 cm in diameter
- Milker's nodules are generally multiple; Orf nodules are generally solitary
- Diagnosis made by history/histologic appearance

## MICROSCOPIC

- Orf and milker's lesions are indistinguishable histologically

- Finger-like acanthosis and pale, vacuolated cytoplasm with eosinophilic inclusion bodies in upper epidermal keratinocytes
- Dilated vessels show infiltration of macrophages, lymphocytes, eosinophils, and plasma cells

## TOP DIFFERENTIAL DIAGNOSES

- Pyogenic granuloma
- Pyoderma gangrenosum
- Herpetic whitlow
- Mycobacterium marinum* infection of skin
- Cutaneous anthrax

Solitary Crusted Lesion of Orf

(Left) Solitary crusted lesion located on the finger is characteristic of orf virus in an individual due to contact with an infected sheep. (Courtesy Geisinger Medical Center Department of Dermatology.) (Right) Multiple blister-like lesions are characteristic of milker's nodule. (Courtesy R. Ceovic, MD, PhD.)

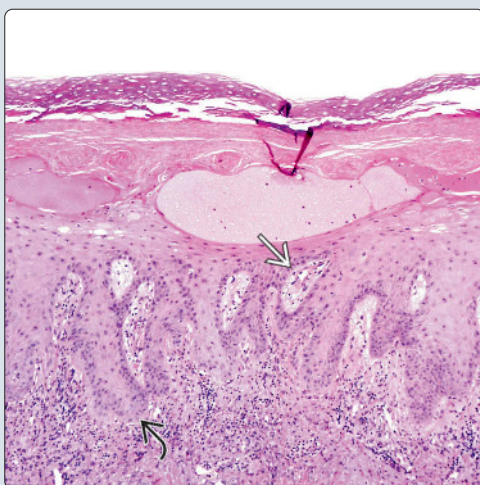


Blister-Like Lesions of Milker's Nodules

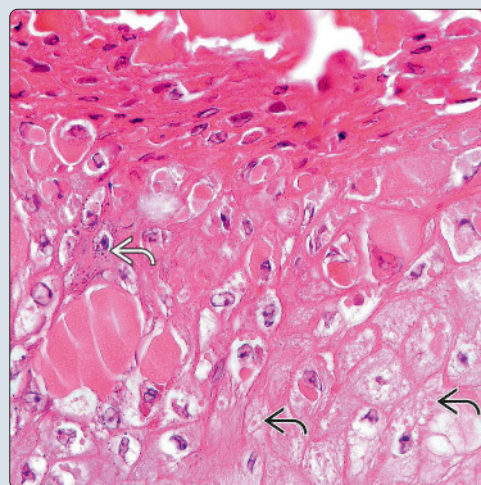


Acanthosis and Mixed Dermal Infiltrate

(Left) Finger-like acanthosis [A], dilated vessels [B] in the dermal papillae, and a mixed dermal inflammatory infiltrate can be seen in both orf and milker's nodule. (Courtesy A. Bowen, MD.) (Right) Upper epidermal keratinocytes in orf display clumping of keratohyaline granules [C], cytoplasmic and nuclear vacuolation, and numerous eosinophilic cytoplasmic inclusion bodies [D]. (Courtesy Geisinger Dermatology.)



Eosinophilic Cytoplasmic Inclusion Bodies





## TERMINOLOGY

### Synonyms

- Orf nodule: Ecthyma contagiosum, contagious pustular dermatosis, scabby mouth disease
- Milker's nodule: Udder pox

### Definitions

- Clinically and histologically similar entities caused by infection with *Parapoxvirus* variants from occupational exposure to farm animals, presenting as red-blue papules that later crust and resolve spontaneously

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- Orf nodules: Orf virus, member of genus *Parapoxvirus*, acquired via human contact with infected sheep/goats with oral lesions
- Milker's nodules: Pseudocowpox virus or paravaccinia virus, member of genus *Parapoxvirus*, acquired via human contact with infected cow udders/oral region of nursing calves

## CLINICAL ISSUES

### Site

- Most commonly on forearm, hand, or fingers; less commonly on face and perianal regions via autoinoculation

### Presentation

- Skin
  - Incubation period: 3-7 days
  - Initial presentation
    - Eruption of well-circumscribed, red-blue papule(s) measuring 1-2 cm in diameter
    - Milker's nodules are generally multiple; Orf nodules are generally solitary
  - Progression through 6 clinical stages, each lasting ~ 1 week
    - Maculopapular stage
    - Target stage: Lesion develops red center surrounded by white ring with red periphery
    - Acute stage: Transformation into weeping nodule
    - Nodular stage: Firm, nontender nodule
    - Papillomatous stage: Papillomas develop on surface
    - Regressive stage: Thick, crusted lesion resolves
- Systemic
  - Occasionally patient develops mild fever, lymphadenitis, &/or lymphangitis
  - Potential complications include maculopapular eruption of trunk, papulovesicular eruption, erysipelas, erythema multiforme-like eruption, and bullous pemphigoid-like eruption
  - Superimposed *Pseudomonas aeruginosa* infection has been reported
  - Giant, persistent lesions may be seen in immunocompromised individuals

### Laboratory Tests

- Diagnosis made by history/histologic appearance
- PCR is used to distinguish between viral subgroups
- Electron microscopy negative contrast demonstrates cylindrical *Parapoxvirus* with convex ends

## Treatment

- Drugs
  - Treatment is symptomatic
  - Infection is not influenced by antibiotics unless complicated with superinfection
- Prevention
  - Good hand hygiene is paramount

## Prognosis

- Majority of patients experience resolution in 4-8 weeks with no scarring

## MICROSCOPIC

### Histologic Features

- Orf/milker's lesions are indistinguishable histologically
- Early lesion
  - Finger-like acanthosis and pale, vacuolated cytoplasm with eosinophilic inclusion bodies in upper epidermal keratinocytes
  - Spongiform degeneration, including wispy eosinophilic strands in cytoplasm, is often present
  - Intranuclear eosinophilic inclusion bodies may be present
  - Dilated vessels show infiltration of macrophages, lymphocytes, eosinophils, and plasma cells
- Later lesion
  - Central epidermal necrosis
  - Neutrophilic infiltrate along borders and within necrotic tissue

## ANCILLARY TESTS

### Immunohistochemistry

- Immunoperoxidase staining using orf-specific monoclonal antibodies confirms diagnosis
- Atypical dermal infiltrate with CD30(+) cells can be seen, although patterns are not entirely consistent
  - Orf nodules can have clusters of CD30(+) cells
  - Milker's nodules can have scattered CD30(+) cells

## DIFFERENTIAL DIAGNOSIS

### Histological

- Pyogenic granuloma: Lesion displays collarette of epidermis; inflammatory infiltrate may be absent if epidermis is intact
- Pyoderma gangrenosum: Mixed cellular infiltrate is mainly neutrophils; erythrocyte extravasation without mural necrosis or luminal fibrin deposition
- Herpetic whitlow: Lacks eosinophilic inclusion bodies in vacuolated cells as seen in orf/milker's nodules
- *Mycobacterium marinum* infection of skin: Acid-fast bacilli in early lesions; pseudoepitheliomatous hyperplasia and hyperkeratosis of epidermis are characteristic
- Cutaneous anthrax: Gram stain reveals gram-positive rod-shaped bacilli; pandermal inflammation

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## KEY FACTS

### TERMINOLOGY

- Viral infection causing vesiculation of oral mucosa as well as skin on hands and feet

### ETIOLOGY/PATHOGENESIS

- Most commonly caused by Coxsackie viruses A16 and A6 as well as enterovirus 71
- Transmitted via contact with bodily fluids

### CLINICAL ISSUES

- Small children most affected (under 4 years of age)
- Typically warmer months (summer and autumn)
- Lesions appear 3-7 days after exposure
- Frequently antecedent viral prodrome
  - Fever, malaise, headache, diarrhea
- Followed by
  - Eruption of oral blisters
    - Lips, inner cheeks, less commonly tongue
  - Erythematous papules on hands and feet

- Progress to vesicles

- May have subsequent onychomadesis

- Transient separation of nail plate

- Other complications may rise in association with hand, foot, and mouth disease (HFMD)

- Coxsackie virus A16: Aseptic meningitis

- Enterovirus A6: Pancreatitis, cerebellar lesions, encephalitis, aseptic meningitis, others

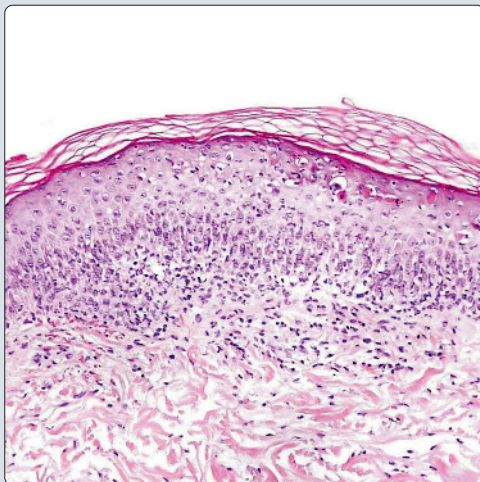
- Same viruses may cause concomitant viral myocarditis

### MICROSCOPIC

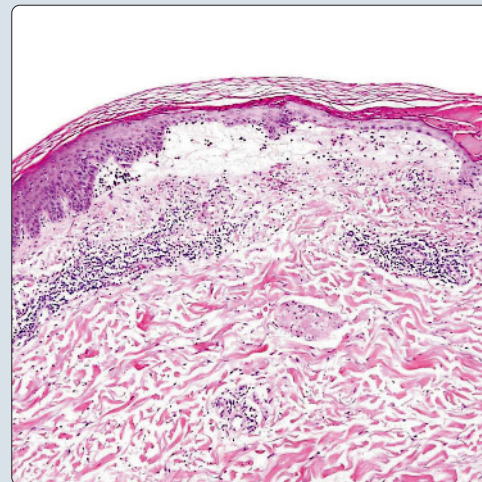
- Intraepidermal blister
  - Secondary to pronounced intercellular edema
- May have keratinocyte apoptosis, dyskeratosis, &/or necrosis
- No characteristic viral inclusions
- May have neutrophilic or lymphocytic inflammatory cell infiltrate
- Papillary dermal edema is feature in some cases

**Early Lesion Without Blister**

*(Left) Early lesions may have significant keratinocyte necrosis with prominent acute inflammation. Blisters may not be evident in the initial stages of infection. (Right) Blisters may be subepidermal, intraepidermal, or even subcorneal. This patient has a subepidermal vesicle.*

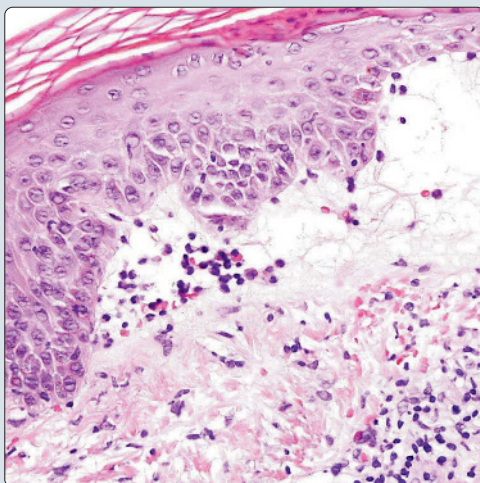


**Blister Formation**

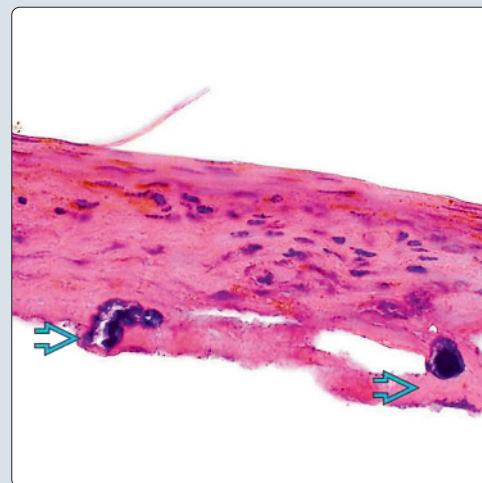


**Paucicellular With Neutrophils**

*(Left) The vesicles are usually paucicellular, and a few neutrophils may be seen. There is a mild underlying lymphocytic infiltrate. (Right) The vesicles may occasionally be impetiginized. In those cases, clusters of bacteria can be found in and around the blister cavity.*



**Impetiginization**





## TERMINOLOGY

### Abbreviations

- Hand, foot, and mouth disease (HFMD)

### Definitions

- Viral infection causing vesiculation of oral mucosa as well as skin on hands and feet

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- Most commonly caused by Coxsackie viruses A16 and A6 as well as enterovirus 71
- Transmitted via contact with bodily fluids
  - Oral and nasal secretions, blood, feces

## CLINICAL ISSUES

### Presentation

- Small children most affected (under 4 years of age)
  - Usually multiple children are affected
- Typically warmer months (summer and autumn)
- Lesions appear 3-7 days after exposure
- Frequently antecedent viral prodrome
  - Fever, malaise, headache, diarrhea
- Followed by
  - Eruption of oral blisters
    - Lips, inner cheeks, less commonly tongue
  - Erythematous papules on hands and feet
    - Progress to vesicles
  - May have subsequent onychomadesis
    - Transient separation of nail plate
  - Trunk or proximal extremities may sometimes be involved
- Other complications may rise in association with HFMD
  - Coxsackie virus A16: Aseptic meningitis
  - Enterovirus A6: Pancreatitis, cerebellar lesions, encephalitis, aseptic meningitis, others
  - Same viruses may cause concomitant viral myocarditis

### Treatment

- Antibiotic ointment may be appropriate to protect against impetigo or other secondary bacterial infection
- Disease does not usually necessitate treatment
- Patients with complicated disease course may require hospitalization and significant supportive care

### Prognosis

- Self-limited disease in most cases
- If other complications arise (e.g., pancreatitis, myocarditis, etc.), significant morbidity and mortality has been recognized

### Prevention

- After recent outbreaks, predominantly in parts of Asia, multiple vaccines have been developed with varying efficacy
  - Predominantly focused on enterovirus 71
    - More severe complications with infection

## MICROSCOPIC

### Histologic Features

- Intraepidermal blister
  - Secondary to pronounced intercellular edema
- May have keratinocyte apoptosis, dyskeratosis, &/or necrosis
- No characteristic viral inclusions
- May have neutrophilic or lymphocytic inflammatory cell infiltrate
- Papillary dermal edema is feature in some cases

## DIFFERENTIAL DIAGNOSIS

### Histopathological

- Orf/milker's nodule
  - Caused by parapoxviruses
  - Significant papillary dermal edema
  - Small eosinophilic intracytoplasmic inclusions
    - May have intranuclear inclusions in early lesions
    - Also cytoplasmic and nuclear vacuolation
  - Marked capillary proliferation and dilatation
- HSV (also in clinical differential)
  - Caused by HSV-1 and HSV-2
  - Lesions more commonly around oral cavity and anogenital area
    - Other areas may be affected (e.g., hands in herpes whitlow)
  - Intraepidermal vesiculation
  - May have epidermal or dermal necrosis
  - Typically large multinucleated cells
    - Nuclei have nuclear molding, ground-glass chromatin, and margination of chromatin to periphery of nucleus
  - Early lesions may have Cowdry A inclusions
- Varicella-zoster virus (VZV; also in clinical differential)
  - Caused by VZV
    - One of herpesviruses
  - Causes chicken pox and zoster
  - Morphological appearance and viral inclusions are identical to those seen with HSV infection
    - Typically large multinucleated cells
      - ◻ Nuclei have nuclear molding, ground-glass chromatin, and margination of chromatin to periphery of nucleus
    - Early lesions may have Cowdry A inclusions

### Clinical

- Molluscum contagiosum
  - Caused by poxvirus
  - Small (< 3 mm) papules with central umbilication
  - Can be found virtually anywhere on body
  - Large eosinophilic or basophilic intracytoplasmic inclusions

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## SECTION 22

# Fungal Infections



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## KEY FACTS

### TERMINOLOGY

- Superficial fungal infection secondary to dermatophytes
- Dermatophytes belong to 3 genera
  - *Trichophyton*, *Epidermophyton*, *Microsporum*

### CLINICAL ISSUES

- Classic lesion
  - Annular plaque of erythema with scale at advancing border

### MICROSCOPIC

- Skin infection
  - Clue
    - Neutrophils in stratum corneum
    - Sandwich sign
      - Parakeratosis or compact orthokeratosis underlying basket-woven stratum corneum (dermatophytes located in between)
  - Fungal stain(s) highlight hyphae

- Majocchi granuloma
  - Fungal hyphae tracking down into hair follicles
- Nail infection
  - Hyphae in nail plate or in subungual debris
- Hair infection
  - Fungal hyphae in or surrounding hair shafts
- Hyphae refractile on hematoxylin and eosin staining; better seen with fungal stains



### ANCILLARY TESTS

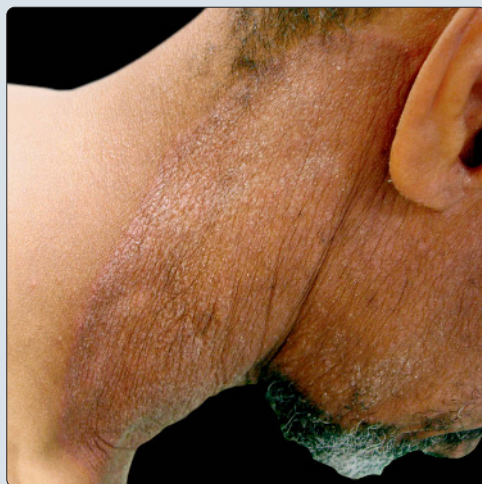
- PAS
- GMS

### TOP DIFFERENTIAL DIAGNOSES

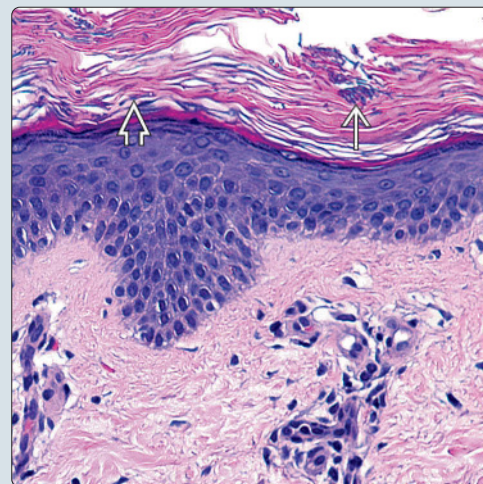
- Other spongiotic/eczematous processes
  - PAS(-)

Scaly Plaque With Lichenification



(Left) There is an erythematous, scaly plaque with lichenification on the neck and jawline of this patient. KOH examination of the scale showed fungal hyphae. (Right) Numerous hyphal structures  are in the hyperkeratotic stratum corneum. Fungi are more obvious where clumped, but often cases are more subtle and similar to foci with nonclumped hyphae . (Courtesy UCSF Dermatopathology Service.)

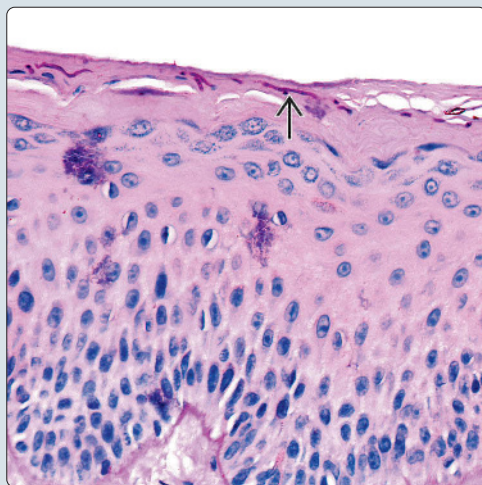


Hyphae in Stratum Corneum

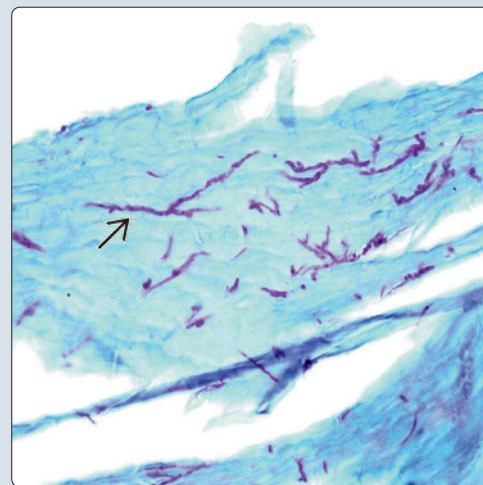


PAS + Fungal Hyphae in Stratum Corneum

(Left) The epidermis is acanthotic with minimal spongiosis. The stratum corneum is compact with PAS(+) fungal hyphae  within it. (Courtesy UCSF Dermatopathology Service.) (Right) In tinea unguium, PAS(+) fungal hyphae  are present in nail plate keratin.



PAS + Hyphae in Nail Plate





## TERMINOLOGY

### Synonyms

- Ringworm, tinea, tinea capitis, tinea faciei, tinea barbae, tinea corporis, tinea cruris, tinea manuum, tinea pedis, tinea unguium, onychomycosis, tinea gladiatorum, tinea imbricata

### Definitions

- Superficial fungal infection secondary to dermatophytes
- Dermatophytes belong to 3 genera
  - *Trichophyton*, *Epidermophyton*, *Microsporum*
- Dermatophytes preferentially infect humans (anthropophilic), animals (zoophilic), or soil (geophilic)
  - Common anthropophilic dermatophytes
    - *Trichophyton rubrum*
    - *Trichophyton violaceum*
- Dermatophytes can infect skin (generally located in stratum corneum), hair (with exception of *Epidermophyton*), &/or nails

## CLINICAL ISSUES

### Presentation

- Classic lesion of tinea corporis or tinea cruris
  - Annular plaque of erythema with scale at advancing border
- Tinea pedis
  - Classic presentation
    - Erythema and scale ± vesicles and pustules that may create moccasin-like sharp demarcation at Wallace line (separates glabrous from nonglabrous skin)
- Tinea capitis
  - Classic presentation in USA: Endothrix (infection of hair shaft itself)
    - Area of alopecia on scalp with broken hairs ("black dot" tinea), generally secondary to *Trichophyton tonsurans*
  - Ectothrix infection: Infection around hair shaft
    - Fluorescence may be seen under Wood lamp examination
    - Commonly secondary to *Microsporum canis*
    - Also *Microsporum audouinii*, *Microsporum distortum*, *Microsporum ferrugineum*
  - Nonanthropophilic dermatophytes cause more inflammatory lesions like favus or kerion
  - Other presentations include abscesses, dissecting cellulitis-like material, and favus (yellow crusts on hair, secondary to *Trichophyton schoenleinii*)
- Tinea incognito
  - Atypical clinical presentations of dermatophytosis
  - Often secondary to use of topical/oral steroids
- Tinea unguium
  - Distal subungual
    - Hyperkeratosis subungually, often with onycholysis or nail dystrophy
    - Most prominent at distal edge of nail
  - Proximal subungual
    - Hyperkeratosis and onycholysis/nail dystrophy
    - Most prominent near cuticle (proximal nail)
  - White superficial

- White macules on surface of nail

- Majocchi granuloma
  - Secondary to infection of hair follicles (usually nonscalp location) with dermatophytes
  - Commonly secondary to *Trichophyton rubrum*
  - Erythematous papules &/or pustules, may coalesce into plaque
  - Preferentially affects lower legs
- Tinea imbricata
  - Infection secondary to *Trichophyton concentricum*
  - Seen in South Pacific/Tropics
  - Concentric, annular, erythematous rings on trunk

### Treatment

- Drugs
  - Oral or topical antifungals

## MICROSCOPIC

### Histologic Features

- Skin infection
  - Clues
    - Neutrophils in stratum corneum
    - Compact orthokeratosis
    - Sandwich sign: Parakeratosis or compact orthokeratosis underlying basket-woven stratum corneum (hyphae located in between)
  - Epidermis shows variable spongiosis
    - May be subtle
    - May be prominent with vesicles or even bullae
    - Rarely subepidermal split/prominent edema
  - Variable mixed inflammatory infiltrate in dermis
- Majocchi granuloma
  - Perifollicular chronic inflammation
  - Fungal hyphae tracking into follicular infundibulum/hair shafts
- Nail infection
  - Hyphae in nail plate or in subungual debris
- Hair infection
  - Fungal hyphae in or surrounding hair shafts
- Hyphae refractile on hematoxylin and eosin staining; better seen with fungal stains

## ANCILLARY TESTS

### Histochemistry

- PAS
  - Bright pink circles and elongated tubules in stratum corneum/nail plate or debris in or around hair shafts
- Gomori methenamine silver
  - Black circles and elongated tubules in stratum corneum/nail plate or debris in or around hair shafts

## DIFFERENTIAL DIAGNOSIS

### Other Spongiotic/Eczematous Processes

- PAS(-)

## SELECTED REFERENCES

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## Majocchi Granuloma

## KEY FACTS

## TERMINOLOGY

- Granulomatous, folliculocentric, nodular, or pustular variant of *tinea* infection

## ETIOLOGY/PATHOGENESIS

- Most commonly caused by *T. rubrum*, less commonly *T. mentagrophytes*, *E. floccosum*

## CLINICAL ISSUES

- Often in areas of shaving (lower legs in women, face in men)
- May be precipitated by preceding use of topical steroids or from bandage occlusion
- More common in immunosuppressed patients

## MICROSCOPIC

- Dermal or perifollicular dermatophytes with ruptured follicles, hair shaft fragments
- Acute and chronic inflammation including granulomatous component, inflammation may be intense and suppurative

- Dermatophytes highlighted on PAS or silver stains

## TOP DIFFERENTIAL DIAGNOSES

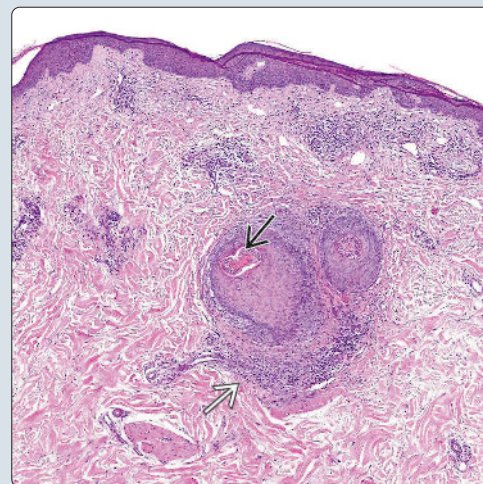
- Bacterial folliculitis
  - Special stains or culture should demonstrate causative bacterial pathogens
- Herpes folliculitis
  - Viral cytopathic changes with absence of deep dermatophytes
- Sarcoidosis, granuloma annulare, and other granulomatous disease
  - Lack of dermatophyte or other infectious organisms, should not demonstrate predominantly perifollicular inflammation, lacks acute suppurative inflammatory infiltrate
- Sweet syndrome
  - Purely neutrophilic infiltrate, often accompanied by fevers, not predominantly perifollicular; scale is not feature of Sweet

## Perifollicular Nodules, Pustules, and Scaling Plaques

(Left) Majocchi presents with a mixture of perifollicular nodules, pustules, and scaling plaques. Legs are commonly affected and often mistreated with steroids, which worsens the disease. Systemic antifungal therapy is required. (Right) On low power, perifollicular inflammation is seen surrounding fragmented hair shafts.

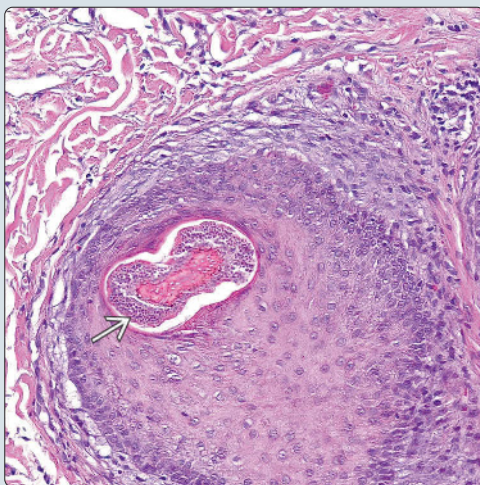


## Perifollicular Inflammation

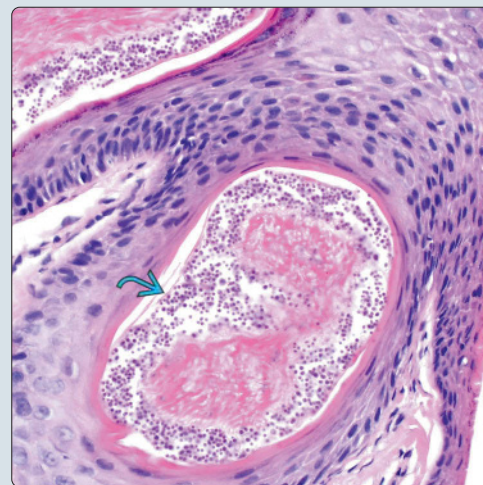


## Fungal Organisms Surrounding Degenerate Hair Shafts

(Left) Numerous fungi surround degenerate hair shafts. (Right) Another case of Majocchi granuloma demonstrates innumerable fungal organisms surrounding a degenerated hair shaft.



## Numerous Fungal Organisms Surrounding Hair Shaft





## TERMINOLOGY

### Synonyms

- Nodular granulomatous perifolliculitis
- Fungal folliculitis

### Definitions

- Granulomatous, folliculocentric, nodular, or pustular variant of tinea infection

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- Most commonly caused by *Trichophyton rubrum*, less commonly *Trichophyton mentagrophytes*, *Epidermophyton floccosum*

## CLINICAL ISSUES

### Presentation

- Perifollicular pustules or nodules, scale may or may not be prominent feature
- Often in areas of shaving (lower legs in women, face in men)
- May be precipitated by preceding use of topical steroids or from bandage occlusion
- More common in immunosuppressed patients

### Treatment

- Drugs
  - Terbinafine: 250 mg daily for 4 weeks in immunocompetent; prolong therapy additional 2-4 weeks if immunocompromised patient
  - Itraconazole pulse therapy: 200 mg twice daily for 1 week, with 2 weeks off therapy; then, repeat cycle for total of 2-3 pulses; itraconazole 200 mg twice daily for 2-3 months has been reported for immunocompromised patients
  - Griseofulvin: 500 mg PO twice daily for 4 weeks
  - Caveat: Does not respond to topical antifungals due to depth of infection

### Prognosis

- Should resolve slowly with therapy

## MICROSCOPIC

### Histologic Features

- Dermal or perifollicular dermatophytes with ruptured follicles, hair shaft fragments
- Acute and chronic inflammation including granulomatous component, inflammation may be intense and suppurative
- Dermatophytes highlighted on PAS or silver stains

## DIFFERENTIAL DIAGNOSIS

### Bacterial Folliculitis

- Special stains or culture should demonstrate causative bacterial pathogens

### Herpes Folliculitis

- Viral cytopathic changes with absence of deep dermatophytes

## Sarcoidosis, Granuloma Annulare, and Other Granulomatous Disease

- Lack of dermatophyte or other infectious organisms, should not demonstrate predominantly perifollicular inflammation, lacks acute suppurative inflammatory infiltrate

## Sweet Syndrome

- Purely neutrophilic infiltrate, often accompanied by fevers, not predominantly perifollicular; scale is not feature of Sweet

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Acute, chronic, and granulomatous infiltrate should create suspicion for infectious etiology
- Diagnosis is confirmed only through demonstration of dermatophytes pathologically or on tissue culture
- Diagnosis may be aided with KOH preparation

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## Onychomycosis

## KEY FACTS

## TERMINOLOGY

- Fungal nail infection, tinea unguium
- Infection of nail plate with either dermatophytes (most common), nondermatophyte moulds, or yeast

## CLINICAL ISSUES

- Onycholysis or hyperkeratotic yellow thickening of distal (most common) nail
- Presents as 1 of 4 subtypes
  - Distal subungual onychomycosis
  - White superficial onychomycosis
  - Proximal subungual onychomycosis
  - Candidal onychomycosis

## MICROSCOPIC

- Often, there is hyperkeratosis with variable amounts of neutrophils
- Presence of fungal forms confirmed by PAS or GMS

## ANCILLARY TESTS

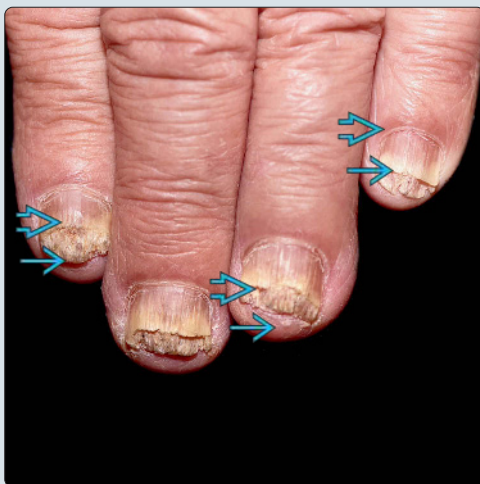
- KOH ± chlorazol black, calcofluor, or PAS and silver stains (GMS) can aid in diagnosis

## TOP DIFFERENTIAL DIAGNOSES

- Trauma
  - Often hemorrhage (extravasated erythrocytes ± hemosiderin) can be identified within nail plate
  - History of trauma (often in runners) with resultant nail dystrophy
- Psoriasis
  - Presence of neutrophils in hyperkeratotic nails with negative PAS, GMS
  - Frequently presents as nail pitting, longitudinal ridging, or crumbling of nails
- Chronic paronychia
  - Variable hyperkeratosis with positive PAS, GMS revealing yeast forms
  - History of frequent hand washing

## Distal Lateral Subungual Onychomycosis

(Left) Fingernails with distal and lateral nail involvement of hyperkeratotic yellow subungual thickening [E] and onycholysis [E], which is characteristic in distal lateral subungual onychomycosis, are shown. (Courtesy R. A. Johnson, MD.) (Right) Hand and foot involvement of a fungal infection shows an annular pink plaque with peripheral scale on the hand [E] (with nail changes) with concomitant tinea pedis [E] and associated onychomycosis [E] of the foot. (Courtesy R. A. Johnson, MD.)

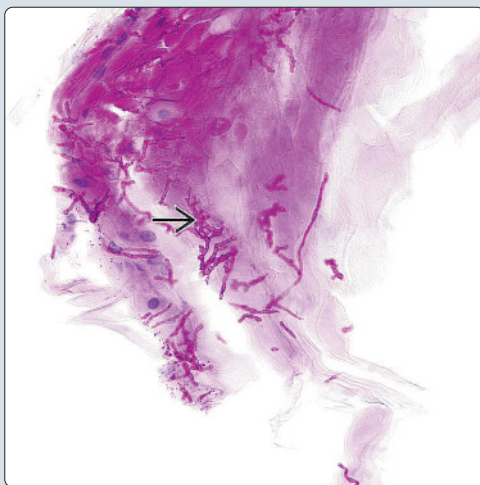


## Tinea Manuum and Onychomycosis

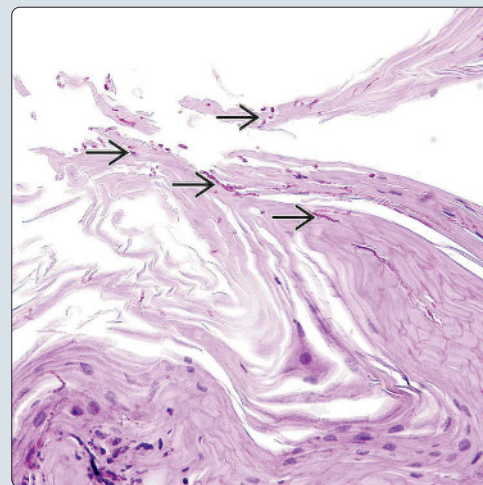


## PAS Demonstrating Fungal Hyphae

(Left) PAS reveals numerous fungal hyphae [E]. (Right) PAS reveals few fungal hyphae [E] piercing the nail plate.



## Fungal Hyphae Within Nail Plate





## TERMINOLOGY

### Synonyms

- Fungal nail infection, tinea unguium

### Definitions

- Infection of nail plate with either dermatophytes (most common), nondermatophyte moulds, or yeast

## CLINICAL ISSUES

### Presentation

- Presents as 1 of 4 subtypes
  - Distal subungual onychomycosis
    - Most common type that involves hyponychium and distal nail bed often presenting as onycholysis or yellow thickening of distal nail
      - *Trichophyton rubrum* is most common
    - In many cases, there may be associated tinea pedis or tinea cruris
    - Sometimes referred to as distal lateral subungual onychomycosis when distal and lateral nail involvement is present
  - White superficial onychomycosis
    - Appears as scattered islands of flaky white or chalky material on dorsal nail plate
      - *Trichophyton mentagrophytes* is most common; however, *T. rubrum*, when diagnosed, can be presenting sign of HIV infection
  - Proximal subungual onychomycosis
    - Appears as leukonychia near lunula, which is frequently due to *T. rubrum* in immunocompromised individuals
  - Candidal onychomycosis
    - Presents as hyperkeratosis with nail bed destruction in patients with mucocutaneous candidiasis (due to *Candida albicans*)
- Children are rarely affected
- Patients are often asymptomatic

### Treatment

- Options, risks, complications
  - Often, there is no long-term risk other than coinfection of adjacent nails
  - Systemic antifungals (terbinafine, fluconazole, itraconazole) are much more effective than topical agents or home remedies (apple-cider vinegar soaks)

### Prognosis

- Often protracted course unless treated with systemic antifungals

## MICROSCOPIC

### Histologic Features

- Often, there is hyperkeratosis with variable amounts of neutrophils
- Hyaline hyphal forms can be seen, but often PAS or GMS stains are used to aid in diagnosis

## ANCILLARY TESTS

### Histochemistry

- KOH ± chlorazol black, calcofluor, or PAS and silver stains (GMS) can aid in diagnosis

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Psoriasis
  - Presence of neutrophils in hyperkeratotic nails with negative PAS, GMS
- Trauma
  - Variable hyperkeratosis with negative PAS, GMS
  - Often hemorrhage (extravasated erythrocytes ± hemosiderin) can be identified within nail plate
- Paronychia (usually chronic)
  - Variable hyperkeratosis with positive PAS, GMS revealing yeast forms

### Clinical

- Trauma
  - History of trauma (often in runners) with resultant nail dystrophy
- Psoriasis
  - Frequently presents as nail pitting, longitudinal ridging, or crumbling of nails
- Paronychia (usually chronic)
  - History of frequent hand washing

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Onycholysis or hyperkeratotic yellow thickening of distal (most common) nail

### Pathologic Interpretation Pearls

- Presence of fungal forms confirmed by PAS or GMS

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# Pityriasis (Tinea) Versicolor

## KEY FACTS

### TERMINOLOGY

- Pityriasis versicolor and tinea versicolor are synonymous

### ETIOLOGY/PATHOGENESIS

- Caused by organisms of genus *Malassezia*

### CLINICAL ISSUES

- Overlaps clinically with several common papulosquamous disorders

### MICROSCOPIC

- Lack of significant inflammation and presence of spores with hyphae in stratum corneum in biopsy from trunk allow discrimination from other common superficial mycoses

### ANCILLARY TESTS

- PAS may be used to highlight fungal elements

### TOP DIFFERENTIAL DIAGNOSES

- Dermatophytosis

- Fewer hyphal elements are present in stratum corneum, and spores are lacking
- Candidiasis
  - Pseudohyphae and yeast are demonstrated within stratum corneum
  - Hyphal invasion of epithelium is frequently present
- Tinea nigra
  - Dematiaceous hyphae, without spores
- Confluent and reticulated papillomatosis
  - Location and demographic are similar, but confluent and reticulated papillomatosis demonstrates undulating hyperkeratosis, marked papillomatosis, follicular plugging, and mild acanthosis

### DIAGNOSTIC CHECKLIST

- Must see hyphal forms to make diagnosis

### Scaly Hyperpigmented Papules and Plaques

(Left) This extensive case of tinea versicolor shows thin, scaly hyperpigmented papules and plaques on the neck.

(Right) Tinea versicolor presents clinically as hyperpigmented macules and patches on the trunk.

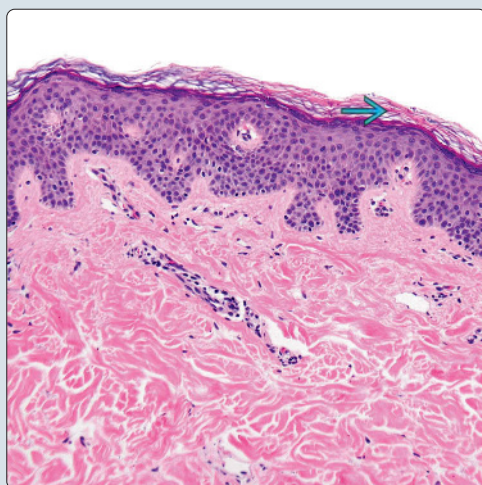


### Hyperpigmented Macules and Patches

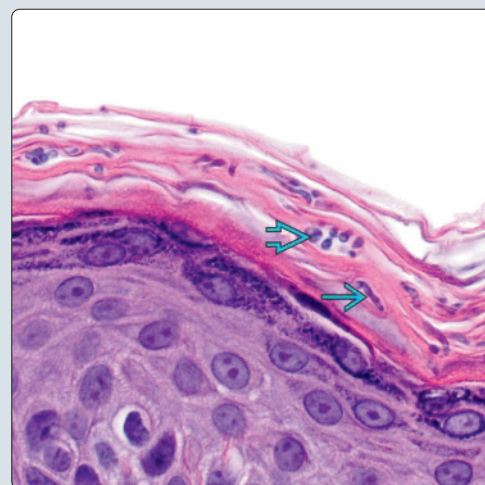


### Low-Power View Resembles Normal Skin

(Left) At low power, the differential diagnosis includes normal skin, given the absence of inflammation. However, parakeratosis and intracorneal fungal elements are identifiable. (Right) Histology demonstrates numerous spores and hyphae in the stratum corneum at high power.



### Spores and Hyphae in Stratum Corneum





## TERMINOLOGY

### Abbreviations

- Tinea versicolor (TV)

### Synonyms

- Pityriasis versicolor and TV are synonymous

### Definitions

- Common, usually asymptomatic superficial mycosis present on trunk of adolescents and adults

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- TV is caused by organisms of the *Malassezia* genus, which are normally commensal but become pathologic when yeast form transforms into mycelia under conditions of heat, sweating, oily skin, or immunosuppression

## CLINICAL ISSUES

### Presentation

- Small patches and plaques with scale and hyperpigmentation or hypopigmentation, most commonly on trunk and shoulders
  - Occasionally involvement of intertriginous areas, and, in younger children, head and neck may be involved
- Postinflammatory pigmentary alteration may become chronic

### Treatment

- Drugs
  - Numerous topical therapies are available for treatment of TV
  - 1st-line topical therapies are ketoconazole 2% (cream or shampoo), terbinafine 1% cream, and ciclopirox olamine 1% cream
  - Evidence also supports use of oral systemic antifungal therapy
  - Most effective treatments are itraconazole (200 mg/day for 5-7 days), fluconazole (300 mg/week for 2 weeks), and pramiconazole (200 mg/day for 2 days)

### Prognosis

- TV is benign but often recurrent condition that responds well to treatment
- However, postinflammatory pigment alteration may become chronic

## MICROSCOPIC

### Histologic Features

- Low-power view is reminiscent of normal skin with only sparse perivascular infiltrate ± hyperkeratosis and mild acanthosis
- Abundant spores and hyphal elements are present in stratum corneum, associated with little or no inflammation
- Of note, biopsies from trunk will often demonstrate spores (without hyphae) in healthy subjects

## ANCILLARY TESTS

### Histochemistry

- PAS is not necessary for diagnosis but may be used to highlight fungal spores and hyphae of *Malassezia*

### KOH Preparation

- Shows short fungal hyphae and groups of spores ("spaghetti and meatballs")

## DIFFERENTIAL DIAGNOSIS

### Dermatophytosis

- Fewer hyphal elements are present in stratum corneum, and spores are lacking
- Most cases have significant (but nonspecific) inflammatory features, which can include
  - Neutrophils in stratum corneum or epidermis, spongiosis or psoriasiform changes, folliculitis, extravasated red blood cells, fibrosis, & occasionally papillary dermal edema

### Candidiasis

- Affected sites include epidermis and mucosal epithelia
- Pseudohyphae and yeast are demonstrated within stratum corneum
  - Pseudohyphae tend to orient perpendicularly to epidermis (vs. hyphae of TV), but this is not steadfast feature
- Hyphal invasion of epithelium is frequently present
- Intraepithelial and intracorneal neutrophilic abscesses are common

### Tinea Nigra

- Dematiaceous hyphae, without spores
- Seen on acral skin

### Confluent and Reticulated Papillomatosis

- Location and demographic are similar, but confluent and reticulated papillomatosis demonstrates undulating hyperkeratosis, marked papillomatosis, follicular plugging, and mild acanthosis
- *Malassezia* yeast can be present in stratum corneum, but hyphae are absent

### Pityriasis Rosea

- May overlap with TV clinically, but significant inflammation is much more typical of pityriasis rosea (PR)
- Most common histopathologic features are focal parakeratosis, dyskeratosis, spongiosis, lymphocytic exocytosis, perivascular lymphocytic infiltrate, and erythrocyte extravasation
- Reaction pattern in PR is spongiotic and is thus deserving of PAS in routine evaluation to exclude dermatophytosis

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Must see hyphal forms to make diagnosis, as yeast are commensal

## SELECTED REFERENCES

1. Hu SW et al: Pityriasis versicolor: a systematic review of interventions. Arch Dermatol. 146(10):1132-40, 2010

## KEY FACTS

## CLASSIFICATION

- Superficial cutaneous mycosis

## ETIOLOGY/PATHOGENESIS

- Caused by pigmented (dematiaceous) fungus, almost always *Hortaea werneckii*

## CLINICAL ISSUES

- Presents as irregularly pigmented patch on acral skin, which is usually interpreted clinically to represent melanoma

## MICROSCOPIC

- Pigmented septate hyphae and spores in superficial aspect of cornified layer
- Fenestrations within cornified layer
- No inflammatory infiltrates

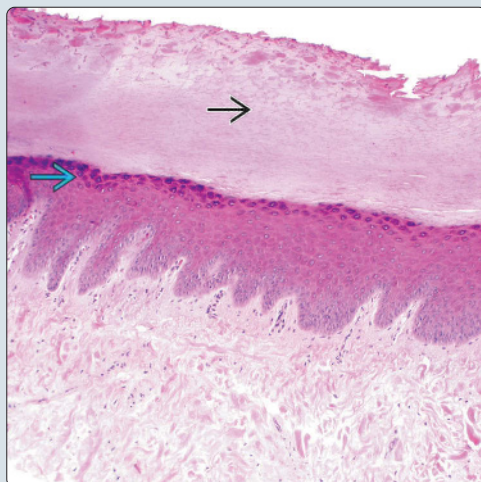
## ANCILLARY TESTS

- Bedside testing (potassium hydroxide preparation of skin scraping) may lead to diagnosis when pigmented hyphae are seen

## TOP DIFFERENTIAL DIAGNOSES

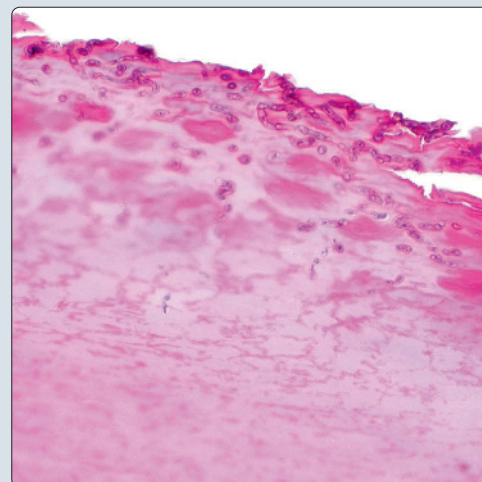
- Other superficial mycoses lack pigment and induce inflammatory change
  - Dermatophytosis usually causes parakeratosis with neutrophils in cornified layer
  - Candida occurs on mucosal epithelium, has hyphae in vertical orientation
- Melanoma or melanoma in situ
  - Mainly clinical differential diagnosis
  - Distinguished histologically by proliferation of atypical melanocytes within epidermis

Hyperkeratosis on Acral Skin

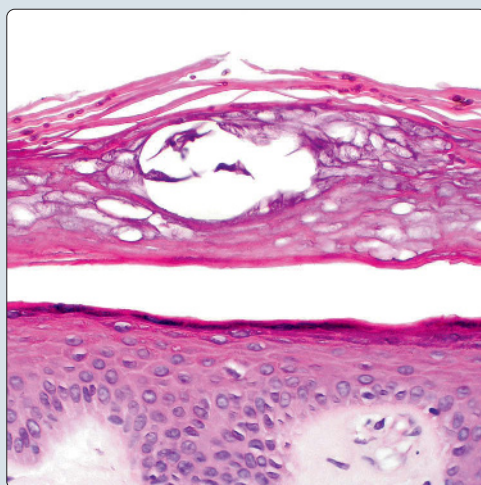


(Left) *Tinea nigra* tends to affect acral skin, which is recognizable by the thick compact cornified layer [1], as well as an epidermis, which is acanthotic with an increased granular cell layer [2]. (Right) High-power view of the cornified layer reveals brown pigmented septate hyphae cut in both longitudinal and transverse dimensions. Hyphae predominate in the most superficial aspect of the stratum corneum.

Pigmented Hyphae in Cornified Layer

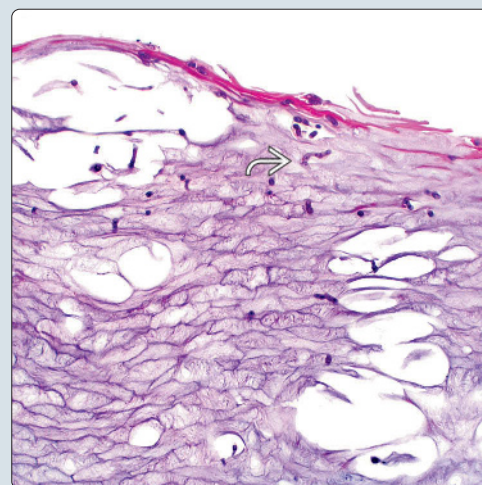


Fenestrations in Cornified Layer



(Left) Fenestrations or perforations in a thickened cornified layer can be seen on scanning magnification and suggest a diagnosis of tinea nigra. (Right) A thickened cornified layer is typical of the acral location of tinea nigra. Additionally, fenestrations within that cornified layer suggest the diagnosis. *Tinea nigra* is confirmed by identifying pigmented hyphae in the cornified layer [3].

Cornified Layer of Tinea Nigra





**TERMINOLOGY****Definitions**

- Superficial cutaneous mycosis caused by *Hortaea werneckii*

**ETIOLOGY/PATHOGENESIS****Infectious Agents**

- Superficial infection of skin by pigment-producing (dematiaceous) fungi
- Nearly all cases are caused by *H. werneckii*
  - *H. werneckii* was formerly known as *Phaeoannellomyces werneckii* and *Exophiala werneckii*
- Rarely other dematiaceous fungi can cause tinea nigra

**CLINICAL ISSUES****Presentation**

- Presents in otherwise healthy individuals, with no predilection for immunocompromised hosts
- More common in coastal regions
- Patients present with acquired pigmented patch on acral skin, either palm or sole
- Lesions are often multicolored, with shades of brown, black, and gray
- Clinical picture is often concerning for acquired melanocytic neoplasm, possibly melanoma

**Treatment**

- Drugs
  - Topical keratolytics may be used (salicylic acid, urea, or ammonium lactate)
  - Topical antifungals (ketoconazole cream) are also effective
  - Highly unusual to require systemic antifungal therapy

**Prognosis**

- Nearly universal response to treatment with topical antifungals

**MICROSCOPIC****Histologic Features**

- Most commonly occurs on acral skin, which is characterized by thick compact cornified layer, stratum lucidum, and hypergranulosis
- Septate hyphae and few spores with light-brown to dark-brown pigment are seen in superficial aspect of cornified layer
- Fenestrations or perforations into cornified layer can be seen on scanning magnification and suggest diagnosis
- Usually no inflammatory cells in cornified layer

**ANCILLARY TESTS****Bedside Testing**

- Skin scrapings prepared with potassium hydroxide reveal pigmented tan-to-brown septate hyphae
- Tape stripping of lesion may also reveal pigmented hyphae
- Dermoscopy can be helpful

**DIFFERENTIAL DIAGNOSIS****Histopathological Features Unique to Tinea Nigra**

- Dermatophyte infection
  - Nonpigmented hyphae and spores in cornified layer
  - Usually has altered cornified layer: Parakeratosis, neutrophils
  - Inflammatory infiltrates in dermis
- Candida
  - Nonpigmented hyphae, pseudohyphae, and spores
  - Neutrophils and parakeratosis in cornified layer
  - Hyphae predominantly seen in vertical orientation
  - Usually on or near mucosal epithelium rather than acral skin
- Melanoma in situ
  - Asymmetric proliferation of atypical melanocytes within epidermis
- Talon noir
  - Hemorrhage in cornified layer on acral skin

**Main Clinical Differential Diagnosis**

- Acral lentiginous melanoma
  - Biopsy easily distinguishes

**DIAGNOSTIC CHECKLIST****Clinically Relevant Pathologic Features**

- Pigment-producing fungal hyphae in cornified layer may lead to false clinical impression of melanocytic neoplasm (nevus or melanoma), which is often initial clinical diagnosis

**Pathologic Interpretation Pearls**

- Lesions predominantly occur on acral skin
- Pigmented hyphae in otherwise normal cornified layer
- Fenestrations within cornified layer suggest diagnosis on scanning magnification

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## KEY FACTS

## TERMINOLOGY

- Common superficial infection of skin and mucous membranes caused by yeasts of genus *Candida*

## ETIOLOGY/PATHOGENESIS

- Candida albicans* is predominant causal organism of most candidal infections

## CLINICAL ISSUES

- Common in groups at risk, such as patients who are immunocompromised
- Various mucosal and cutaneous manifestations of which oral thrush and candidal intertrigo are most common
- Other forms include chronic mucocutaneous candidiasis, genital candidiasis, candidal paronychia and onychomycosis, congenital candidiasis, and disseminated candidiasis

## MICROSCOPIC

- Neutrophils scattered in epidermis with formation of spongiform or subcorneal pustules

- Orthokeratosis and parakeratosis
- Pseudohyphae and spores
  - Blue streaks oriented perpendicular to skin surface
  - Mostly in zones of parakeratosis



## ANCILLARY TESTS

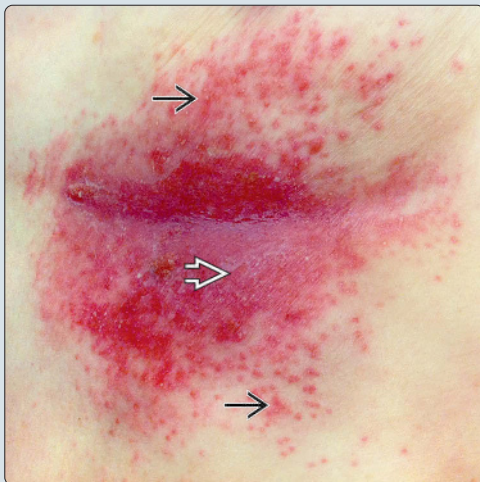
- Fungal elements best visualized with PAS stain

## TOP DIFFERENTIAL DIAGNOSES

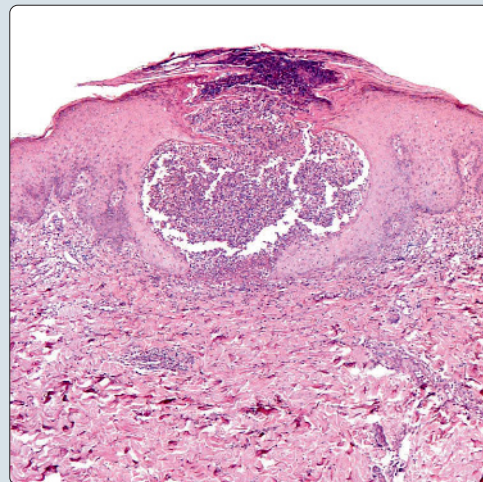
- Dermatophytosis
  - Septate and branching hyphae in stratum corneum
- Inverse psoriasis
  - Devoid of fungal elements
- Tinea versicolor
  - Shorter hyphae and round or oval spores ("spaghetti and meatballs") in normal cornified layer with minimal inflammation

Red Macerated Papules and Plaques


(Left) Red, moist, glistening, macerated papules and plaques  and satellite pustules  located in a submammary fold are typical for candidal intertrigo. (Right) Biopsy taken from a satellite pustule shows a subcorneal and intraepidermal pustular dermatitis. Similar findings can be seen in psoriasis and dermatophytosis.

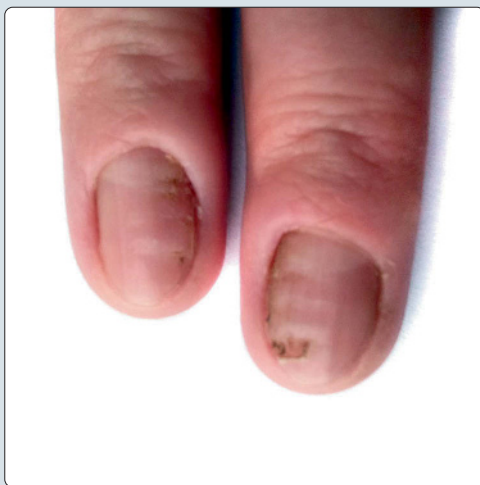


Subcorneal and Intraepidermal Pustule

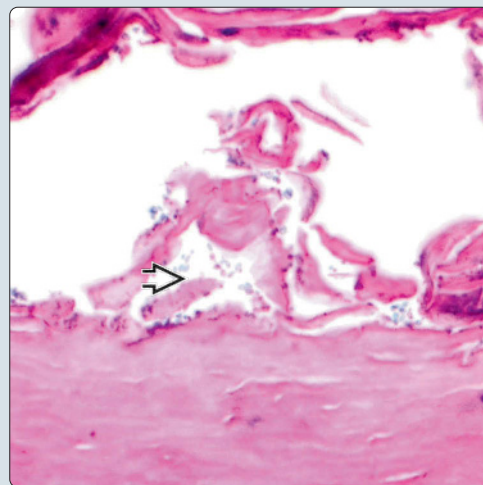


Redness and Swelling With Onycholysis

(Left) Redness and swelling of the paronychia area with onycholysis and transverse ridging of the nail plates are characteristic findings of candidal paronychia. (Right) A nail plate biopsy of candidal onychomycosis shows numerous spherical or oval yeast cells .



Spherical and Oval Yeast Cells





**TERMINOLOGY****Synonyms**

- Candidiasis
- Moniliasis
- Thrush
- Oidiomycosis

**Definitions**

- Common superficial infection of skin and mucous membranes caused by yeasts of genus *Candida*

**ETIOLOGY/PATHOGENESIS****Infectious Agents**

- *Candida albicans* is predominant causal organism of most candidal infections
  - Oval yeast 2-6 x 3-9  $\mu\text{m}$  in size
  - Produce budding cells, pseudohyphae, and true hyphae
- Other species, including *Candida krusei*, *Candida glabrata*, *Candida dubliniensis*, and *Candida inconspicua* isolated from severely immunocompromised patients

**Pathogenesis**

- *C. albicans* is not normal cutaneous saprophyte but usually colonizes oropharynx, gastrointestinal tract, and vagina
- Alteration in host defenses, either localized or generalized, allows organism to become pathogenic
  - Factors predisposing to infection include
    - Mechanical factors (trauma, occlusion)
    - Nutritional factors (iron deficiency, malnutrition)
    - Physiologic alteration (menses, pregnancy)
    - Systemic illnesses (diabetes mellitus, malignancy, uremia, immunodeficiency states)
    - Iatrogenic causes (antibiotics, steroids)
  - Virulence factors include surface adhesion molecules and proteinase enzymes

**CLINICAL ISSUES****Epidemiology**

- Incidence
  - Common in groups at risk (immunocompromised patients)
- Age
  - Any age
- Sex
  - Both sexes

**Presentation**

- Various mucosal and cutaneous manifestations
- Oral candidiasis may appear in acute or chronic forms
  - Acute pseudomembranous candidiasis or thrush
    - Most common form of oral candidiasis
    - Occurs in neonates or in adults usually secondary to local or general predisposing factors
    - Discrete white patches on buccal mucosa, tongue, palate, and gingivae, which, when removed, leave raw and brightly erythematous surface
  - Acute erythematous (atrophic) candidiasis
    - May occur de novo or after sloughing of pseudomembrane

- Commonly associated with antibiotics and steroid treatments
- Marked soreness and depapillated erythematous areas on dorsal surface of tongue
- Chronic pseudomembranous candidiasis
  - Occurs principally in immunocompromised patients
  - Very persistent lesions
  - Very similar clinically to acute pseudomembranous form
- Chronic erythematous candidiasis (denture stomatitis)
  - Associated with loss of dentition, poorly fitting dentures, malocclusion, and vitamin deficiency
  - Erythema and edema of palatal mucosa that contacts dentures
- Chronic plaque-like candidiasis (hyperplastic candidiasis, candidal leukoplakia)
  - Smokers particularly prone to develop this form
  - Very persistent, firm, irregular white plaques
  - Must be differentiated from other types of leukoplakia
- Chronic nodular candidiasis
  - Cobbled appearance of tongue usually in patients with chronic mucocutaneous candidiasis
- Angular cheilitis (perlèche, angular stomatitis)
  - Persistent salivation, lip licking, and sagging skin at oral commissure are predisposing factors
  - Erythema, fissuring, maceration, and soreness at angles of mouth
  - Often associated with chronic atrophic candidiasis
- Median rhomboid glossitis
  - Variant of chronic plaque-like candidiasis
  - Central papillary atrophy of dorsal surface of tongue
- Candidiasis of skin and genital mucous membranes
  - Candidal intertrigo (flexural candidiasis)
    - Most common clinical presentation of candidiasis on glabrous skin
    - Any skin fold may be involved
    - Pruritic, erythematous, macerated plaques with satellite pustules
    - Diaper candidiasis and erosio interdigitalis blastomycetica are particular forms of candida intertrigo
  - Vulvovaginitis (vulvovaginal thrush)
    - Thick, abundant, cream-colored discharge with associated vaginal erythema, edema, pustules, and erosions
    - Increased in pregnancy
  - Candidal balanitis
    - Small papules or fragile papulopustules on glans or in coronal sulcus
  - Nodular and granulomatous candidiasis of napkin area (granuloma gluteale infantum)
- Candidal paronychia
  - Redness, swelling, and tenderness of nail fold
  - Secondary nail changes include onycholysis and transverse ridging and discoloration of nail plate
- Candidal onychomycosis
  - May present as distal onycholysis or complete destruction of nail plate and may be associated with paronychia
- Congenital candidiasis

- Candidiasis of skin and mucous membranes present at time of birth, following intrauterine infection
- Macules, papules, vesicles, and pustules, predominantly on upper half of body and on palms and soles
- Chronic mucocutaneous candidiasis
  - Heterogeneous group of clinical syndromes characterized by chronic, treatment-resistant, superficial candidal infections of skin, nail, and oropharynx
  - Associated conditions include endocrinopathies, diabetes mellitus, iron deficiency, vitiligo, pernicious anemia, thymoma, and recurrent infections
- Disseminated (systemic) candidiasis
  - Occurs in immunosuppressed patients
  - Organs most commonly involved include lungs, spleen, kidneys, liver, heart, and brain
  - Skin lesions include erythematous papulonodules on trunk and extremities and necrotic cutaneous lesions resembling ecthyma gangrenosum

### Laboratory Tests

- KOH preparation and culture of yeast of *Candida* on Sabouraud medium are confirmatory
- Hematologic tests can be important when associated with HIV infection, diabetes, blood dyscrasias, or nutritional deficiencies
  - Blood folate, vitamin B-12, serum ferritin, glucose, hemoglobin, lymphocytes, and WBC counts
  - Lymphocyte function, serum immunoglobulins, calcium status, parathyroid hormone level, and HIV testing in chronic mucocutaneous candidiasis

### Treatment

- Options, risks, complications
  - Strategy is to eliminate pathogenic organism and to correct factors that predispose patients to candidal infections
- Adjuvant therapy
  - Soak in dilute Burow solution 1:20 2x daily for 15 minutes
- Drugs
  - Imidazole cream applied 2x daily, or nystatin ointment 3x daily
  - Oral fluconazole 150-200 mg/day for 1 week (for severe, unresponsive cases)
    - For HIV-infected patients, maintenance therapy with fluconazole for 2-3 weeks

### Prognosis

- Mucocutaneous candidiasis carries excellent prognosis
- Systemic candidiasis is correlated with degree of immunosuppression and carries high mortality rate

## MICROSCOPIC

### Histologic Features

- Mucocutaneous candidiasis
  - Perivascular and interstitial mixed-cell infiltrate of lymphocytes and neutrophils
  - Neutrophils scattered in epidermis with formation of spongiform or subcorneal pustules
  - Variably acanthotic epidermis, more pronounced in chronic forms
  - Orthokeratosis and parakeratosis

- Pseudohyphae and spores
  - Mostly in zones of parakeratosis
  - Blue streaks oriented perpendicular to skin surface
  - May be sparse, especially in pustules
  - Best visualized with special stains
- Disseminated candidiasis
  - Small abscesses in dermis
  - Leukocytoclastic vasculitis
  - Mild perivascular mixed-cell inflammatory infiltrate
  - Budding yeasts may be found in dermis, even in vessel walls

### Cytologic Features

- Spherical or oval yeast cells, budding cells, pseudomycelium of nonbranching filamentous cells

## ANCILLARY TESTS

### Histochemistry

- Periodic acid-Schiff
  - Reactivity: Positive
- Grocott methenamine silver
  - Reactivity: Positive

## DIFFERENTIAL DIAGNOSIS

### Dermatophytosis

- More annular and scaly than pustular
- Can be indistinguishable histopathologically
- Septate and branching hyphae located especially at interface between abnormal cornified layer and original stratum corneum, in zones of compact orthokeratosis (sandwich sign)

### Inverse Psoriasis

- May be indistinguishable clinically and histopathologically from candidiasis
- Devoid of fungal elements

### Tinea Versicolor

- Different clinical aspects
- Shorter hyphae and round or oval spores ("spaghetti and meatballs") in normal cornified layer with minimal inflammation

### Other Entities

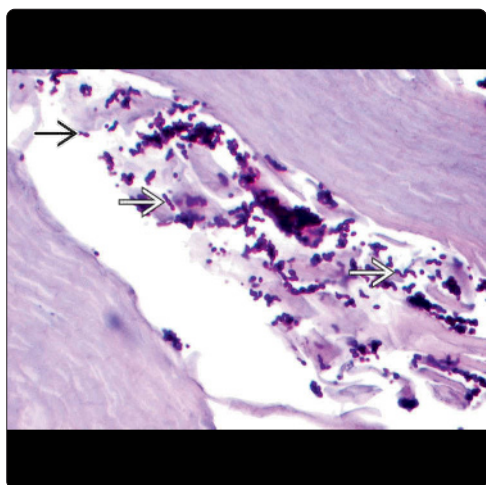
- Bacterial intertrigo, erythrasma
- Contact dermatitis, seborrheic dermatitis
- Familial benign pemphigus, flexural Darier disease, acrodermatitis enteropathica

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**Budding Cells and Pseudohyphae**

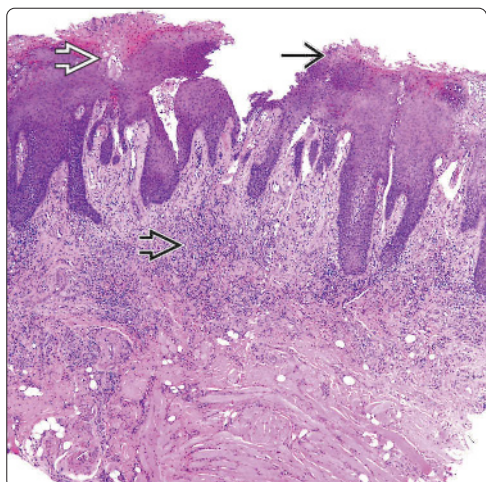


**Erythematous, Atrophic Candidiasis**

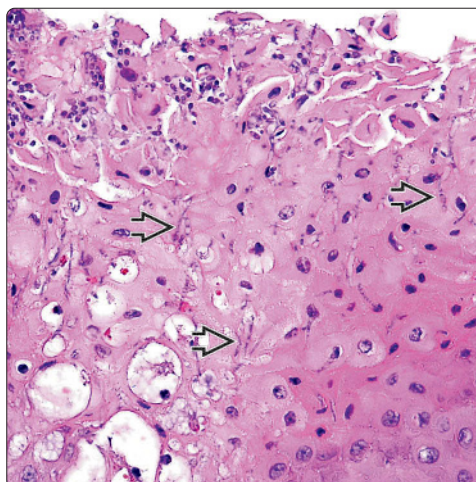


(Left) Budding cells and pseudohyphae of *Candida* are best visualized with a PAS stain. (Right) Clinical photograph shows an acute erythematous (atrophic) candidiasis in an immunosuppressed patient due to steroid therapy.

**Acanthosis, Parakeratosis, and Mixed Dermal Infiltrate**

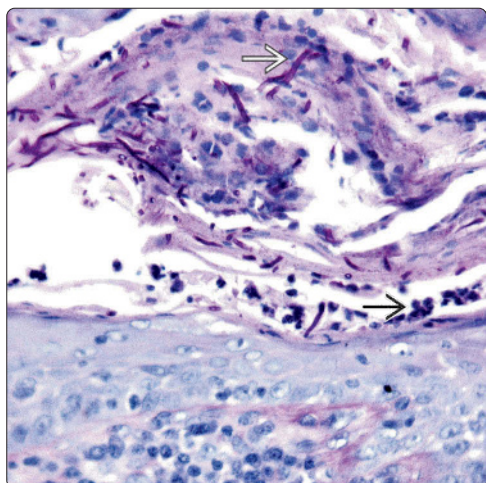


**Pseudohyphae Perpendicular to Epidermis**

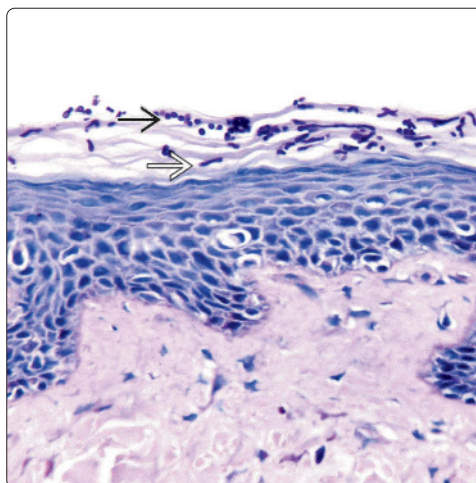


(Left) Biopsy from a lesion of oral thrush shows perivascular and interstitial mixed-cell infiltrate of lymphocytes accompanied by neutrophils, spongiosis in an acanthotic epithelium, neutrophils scattered in the epithelium, and parakeratosis. (Right) Pseudohyphae of *Candida* in the cornified layer are apparent as blue streaks oriented nearly perpendicular to the skin surface.

**Dermatophytosis With Septate, Branching Hyphae**



**Tinea Versicolor With Shorter Hyphae and Oval Spores**



(Left) Neutrophils in the stratum corneum should prompt search for fungal elements. Presence of septate and branching hyphae differentiate this case of dermatophytosis from candidiasis. (Right) Unlike candidiasis, tinea versicolor is typified by shorter hyphae and round or oval spores ("spaghetti and meatballs") in a normal cornified layer with minimal inflammation.



## KEY FACTS

## TERMINOLOGY

- Granulomatous subcutaneous mycotic infection caused by *Sporothrix schenckii*

## CLINICAL ISSUES

- Lymphocutaneous/ascending nodular lymphangitis sporotrichosis
- Fixed cutaneous sporotrichosis
- Multifocal (disseminated) cutaneous sporotrichosis

## MICROSCOPIC

- Granulomatous inflammation with inflammatory infiltrate and central abscess formation
- Initially, suppurative inflammation with high fungal organism load
- Over 4 weeks, plasma cell infiltrate and well-defined granulomas develop

- Granulomas present in majority of cases, most poorly formed, and characteristically suppurative pyogranulomas or sporotrichotic granulomas with peripheral encasing inflammatory infiltrate and central abscess formation

- Asteroid bodies may be seen in granulomas
- Ultimately, increase in lymphocytic inflammation with decrease in fungal organism burden and neutrophilic inflammation is evident

## ANCILLARY TESTS

- Culture is gold standard for definitive diagnosis

## TOP DIFFERENTIAL DIAGNOSES

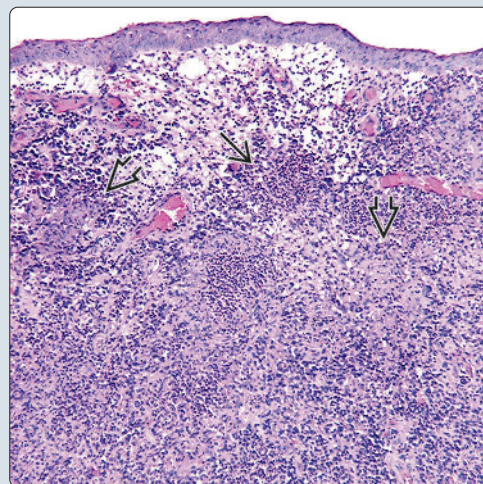
- Other infectious processes
  - Nocardia*, leishmaniasis, chromoblastomycosis, blastomycosis, primary syphilis, atypical mycobacterial infections, *M. tuberculosis*, granuloma annulare, bacterial pyoderma, foreign body granuloma, and chronic staphylococcal ecthyma

**Linear Red Nodules Along Lymphatic Drainage Lines**

(Left) Lymphocutaneous sporotrichosis typically presents as linear red nodules along the lines of lymphatic drainage. This lesion was on the forearm in a patient who tended roses in her garden. (Right) Low-power view of sporo shows suppurative inflammation with a mixed inflammatory infiltrate [1] and poorly formed granulomas [2]. (Courtesy L. Thompson, MD.)

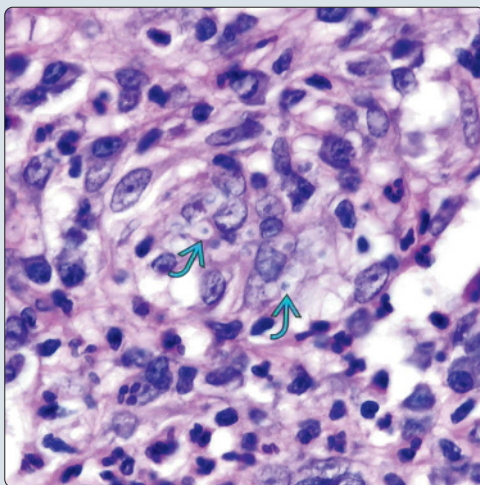


**Mixed Suppurative Inflammatory Infiltrate**

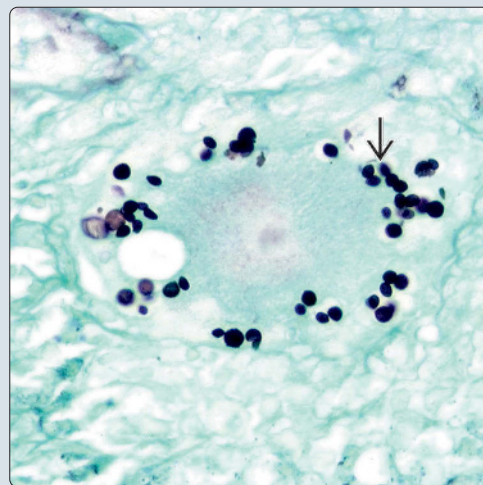


**Yeast Cells Within Histiocytes**

(Left) High-power view of sporotrichosis shows yeast forms [1] within a multinucleated giant cell superimposed on mixed cell inflammation. (Courtesy L. Thompson, MD.) (Right) High-power view of sporotrichosis shows yeast forms [2] within a large, multinucleated giant cell. (Courtesy L. Thompson, MD.)



**Yeast Forms Within Multinucleated Giant Cell**





**TERMINOLOGY****Abbreviations**

- Sporotrichosis (sporo)

**Synonyms**

- *Sporothrix schenckii*, *Sporothrix schenckii* complex, rose gardener disease

**Definitions**

- Sporadic, chronic granulomatous subcutaneous mycotic infection caused by thermally dimorphic fungus *S. schenckii*

**ETIOLOGY/PATHOGENESIS****Environmental Exposure**

- Transmission occurs via traumatic inoculation of fungus by thorns, splinters, scratches, etc.
  - Zoonotic transmission has been reported (rodents, parrots, cats, horses, armadillos)

**Infectious Agents**

- *S. schenckii*
  - Thrives in organic material (sphagnum moss, rotten vegetation, timber, wood, soil, hay)

**CLINICAL ISSUES****Epidemiology**

- Incidence
  - Infection rate of 1 case per 1,000 population in rural areas
  - Occurs worldwide, but endemic in temperate areas (25-28°C) with 80-95% humidity
- Age
  - Typically healthy adults < 30 yr
  - Agriculturalists, foresters, and gardeners at increased risk secondary to exposure

**Presentation**

- **Cutaneous sporotrichosis**
  - Lymphocutaneous/ascending nodular lymphangitis sporotrichosis
    - Most common form (~ 75% of cases)
    - Immunocompetent patients affected, usually upper and lower limbs; bilateral involvement rare
    - Localized, indurated papule 2-4 cm in diameter; develops 7-30 days after inoculation
    - Progressive induration, nodule formation, and ulceration (sporotrichotic chancre)
    - Subsequent lesions develop proximally along lymphatics
    - Mild systemic symptoms sometimes; regional lymphadenopathy often
  - Fixed cutaneous sporotrichosis
    - Face, neck, trunk, or legs affected
    - Localized, asymptomatic, erythematous papuloplaque, papulopustule, nodular, ulcerated, or verrucous plaques
    - No lymphatic dissemination
  - Multifocal (disseminated) cutaneous sporotrichosis
    - Very rare and usually in immunocompromised patients (diabetics, alcoholics, HIV positive, etc.)

- **Extracutaneous sporotrichosis**

- Occurs by inhalation of spores and hematologic dissemination
- May involve osteoarticular joints, lungs, meninges, skeleton, eye, larynx, or genitourinary organs
- Meningeal disease is most severe

**MICROSCOPIC****Histologic Features**

- Nonspecific features with diffuse, chronic granulomatous dermatitis
- Pseudocarcinomatous epidermal hyperplasia and hyperkeratosis often present
- Initially, suppurative inflammation with high fungal organism load
- Over 4 weeks, plasma cell infiltrate and well-defined granulomas develop
  - Granulomas present in majority of cases, most poorly formed, and characteristically suppurative pyogranulomas or "sporotrichotic granulomas" with peripheral encasing inflammatory infiltrate and central abscess formation
- Asteroid bodies may be seen in granulomas
  - Sporothrix asteroid body (SAB): 12-35 µm, extracellular, round budding yeast form surrounded by eosinophilic spicules, usually seen in center of abscess
- Ultimately, increase in lymphocytic inflammation with decrease in fungal organism burden and neutrophilic inflammation is evident

**ANCILLARY TESTS****Microbiology**

- Culture is gold standard for definitive diagnosis
  - Sabouraud dextrose agar (SDA) or potato dextrose agar in 3-5 days
  - Initial colonies: Raised, moist, smooth, cream-colored
  - Older colonies: Leathery, brown-black appearance

**Morphology**

- Yeast/parasitic form: Pleomorphic with spindle-shaped or ovoid cells resembling cigar

**DIFFERENTIAL DIAGNOSIS****Other Infectious Processes**

- *Nocardia*, leishmaniasis, chromoblastomycosis, blastomycosis, primary syphilis, atypical mycobacterial infections, *M. tuberculosis*, granuloma annulare, bacterial pyoderma, foreign body granuloma, and chronic staphylococcal ecthyma
  - Culture, demonstration of characteristic organismal morphology with special stains and clinical history of paramount importance to differentiate

**SELECTED REFERENCES**

1. Rodrigues AM et al: Molecular diagnosis of pathogenic sporothrix species. *PLoS Negl Trop Dis*. 9(12):e0004190, 2015
2. Quintella LP et al: Histopathology of cutaneous sporotrichosis in Rio de Janeiro: a series of 119 consecutive cases. *J Cutan Pathol*. 38(1):25-32, 2011
3. Zhang YQ et al: Sporotrichosis: clinical and histopathological manifestations. *Am J Dermatopathol*. 33(3):296-302, 2011

## Coccidioidomycosis

## KEY FACTS

## ETIOLOGY/PATHOGENESIS

- Lesions caused by dimorphic fungi *Coccidioides immitis* and *Coccidioides posadasii*

## CLINICAL ISSUES

- Initial primary cutaneous lesion is chancriform, painless, indurated nodule or plaque with central ulceration
- Disseminated cutaneous lesions can have protean clinical morphology

## MICROSCOPIC

- Granulomatous acute and chronic dermal inflammatory infiltrate is seen in almost all cases
- Organisms are large spherules varying in size from 5-80  $\mu\text{m}$  within giant cells or free within tissue and occasionally with endospores in larger spherules
  - Endospores are 5-10  $\mu\text{m}$  in size and often numerous
- Pseudoepitheliomatous hyperplasia is often seen (1/3 of cases in one large series)

- Ulceration present in ~ 1/2 of biopsies



## ANCILLARY TESTS

- Coccidioides* antibodies by ELISA (IgG/IgM)
  - Can help detect current or past infection
- Culture
  - More sensitive than biopsy and gold standard for identification

## TOP DIFFERENTIAL DIAGNOSES

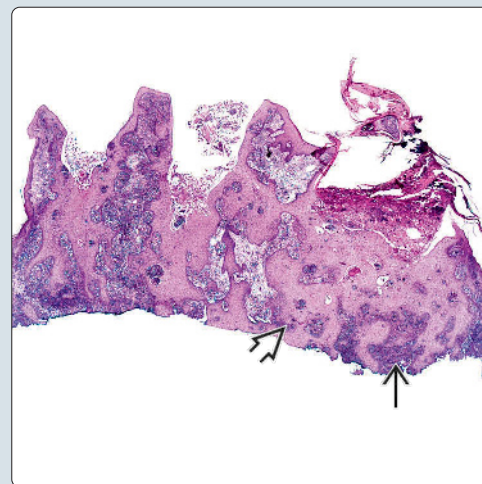
- Other granulomatous infectious skin diseases
  - Other organisms often have characteristic morphology on H&E &/or characteristic geographic distribution
- Myospherulosis
  - Capsule ~ 1  $\mu\text{m}$  thick and spherules do not stain with GMS or PAS (in contrast to *Coccidioides* species)
- Rhinosporidiosis
  - Fungal spherules are much larger (up to 300  $\mu\text{m}$ ) and have thicker walls

Red Nodular Lesion



(Left) This case of disseminated coccidioidomycosis demonstrates a red nodular lesion on the arm. Disseminated lesions can have a protean clinical morphology. (Right) A low-power view of a biopsy of coccidioidomycosis demonstrates significant acanthosis and pseudoepitheliomatous hyperplasia  with dense, diffuse dermal granulomatous inflammation .

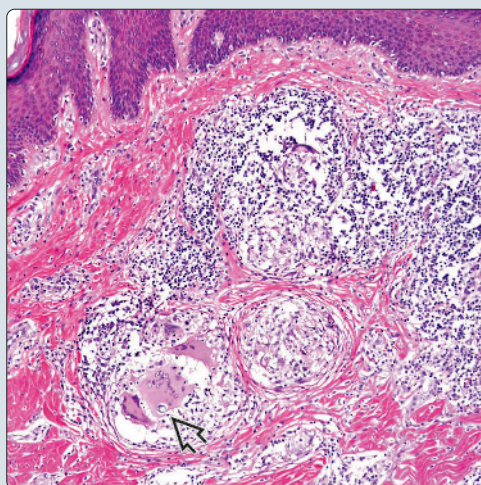


Pseudoepitheliomatous Hyperplasia

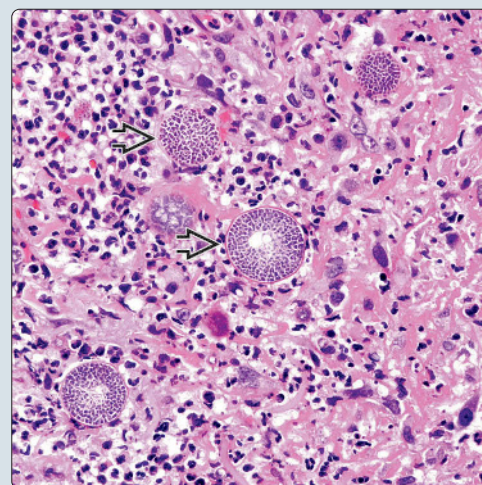


Spore Within Multinucleated Giant Cell

(Left) Even on lower power, one can appreciate a large spore  of coccidioidomycosis within a giant cell in the dermis of this biopsy. (Right) Another skin biopsy of coccidioidomycosis demonstrates several large fungal spores  containing numerous small endospores amidst acute and chronic inflammation in the dermis.



Multiple Spores Containing Endospores





## TERMINOLOGY

### Synonyms

- Valley fever, San Joaquin Valley fever, cocci, desert fever, desert rheumatism

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- Lesions caused by dimorphic fungi *Coccidioides immitis* and *Coccidioides posadasii*
- Occurs in southwestern USA, northern Mexico, and parts of Central and South America

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Primary cutaneous disease is quite rare
    - ~ 1-2% of all cases with only 20 or so case reports in literature
  - Risk and severity of disseminated cutaneous disease is increased in immunosuppressed patients
- Ethnicity
  - No clear racial, gender, or age predilection reported for primary pulmonary coccidioidomycosis
    - Risk of fulminant disease and dissemination is markedly increased in Filipinos and African Americans

### Presentation

- Systemic symptoms from infection include malaise, fever, and arthralgias
  - Most cases are limited to lungs and due to inhalation of arthroconidia
- Initial primary cutaneous lesion is chancreiform, painless, indurated nodule or plaque with central ulceration
  - Incubation period is typically 1-3 weeks
  - Initial lesion typically resolves in matter of weeks unless patient is immunocompromised
  - Regional lymphadenitis or lymphadenopathy ± sporotrichoid-like nodules is common
- Disseminated cutaneous lesions can have protean clinical morphology
  - Lesions can appear papular, pustular, vesicular, nodular, macular, plaque-like, ulcerative, verrucous, &/or cystic
  - Lesions can be single or multiple and affect almost all areas of body

### Treatment

- For disseminated cocci, azole antifungals are 1st line (ketoconazole, fluconazole, or itraconazole)

### Prognosis

- Primary cutaneous lesions often resolve spontaneously
- Disseminated cutaneous lesions improve with treatment of underlying condition

## MICROSCOPIC

### Histologic Features

- Granulomatous acute and chronic dermal inflammatory infiltrate is seen in almost all cases

- Dermal or subcutaneous inflammation may be granulomatous (necrotizing or sarcoidal), neutrophilic, or lymphoplasmacytic
  - Eosinophils range from absent to numerous
- Ulceration present in ~ 1/2 of biopsies
  - In ulcerated lesions, organisms are commonly located in crust
- Pseudoepitheliomatous hyperplasia is often seen (1/3 of cases in one large series)
- Organisms are large spherules varying in size from 5-80 µm within giant cells or free within tissue and occasionally with endospores in larger spherules
  - Endospores are 5-10 µm in size and often numerous

## ANCILLARY TESTS

### Serologic Testing

- Coccidioides* antibodies by ELISA (IgG/IgM)
  - Can help detect current or past infection
- Coccidioides* antibodies by complement fixation
  - Titers > 1:2 generally considered positive
- Coccidioides* antibodies by immunodiffusion
  - Often reported as either positive or negative
- Negative serologic results do not rule out current infection

### Special Stains

- GMS or PAS stains can help highlight organisms (capsule and endospores)

### KOH Mounts

- Typically done on sputum; may be helpful in disseminated cutaneous cases

### Culture

- More sensitive than biopsy and gold standard for identification

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Other granulomatous infectious skin diseases
  - Other organisms often have characteristic morphology on H&E &/or characteristic geographic distribution
- Myospherulosis
  - Not truly infectious disease: Most often idiopathic granulomatous reaction to retained petroleum-based products after surgery
  - Capsule ~ 1 µm thick and spherules do not stain with GMS or PAS (in contrast to *Coccidioides* species)
- Rhinosporidiosis
  - Fungal spherules are much larger (up to 300 µm) and have thicker walls
    - Larger and more numerous endospores
  - Primarily infection of nose

## SELECTED REFERENCES

- Garcia Garcia SC et al: Coccidioidomycosis and the skin: a comprehensive review. *An Bras Dermatol*. 90(5):610-9, 2015
- Carpenter JB et al: Clinical and pathologic characteristics of disseminated cutaneous coccidioidomycosis. *J Am Acad Dermatol*. 62(5):831-7, 2010
- DiCaudo DJ: Coccidioidomycosis: a review and update. *J Am Acad Dermatol*. 55(6):929-42; quiz 943-5, 2006

## KEY FACTS

## CLINICAL ISSUES

- Skin involvement can be primary or secondary
- Solitary nodules that break down and ulcerate are common in primary cutaneous form
- Molluscum contagiosum-like umbilicated papules of varying size present in patients with disseminated disease

## MICROSCOPIC

- 2 main histopathological patterns
  - Gelatinous type: Numerous budding yeasts with marked variation in size and shape, in foamy stroma with little or no inflammation
  - Granulomatous type: Fewer, smaller organisms and mixed suppurative granulomatous infiltrate of histiocytes, lymphocytes, and giant cells with varying degrees of necrosis
- Molluscum-like lesions show dome-shaped area made up of acanthotic epidermis with transepidermal and transfollicular elimination of *Cryptococcus neoformans*

- Inflammatory cells and necrotic dermal debris, including necrobiotic collagen and fragments of capsular material, are present in dermis

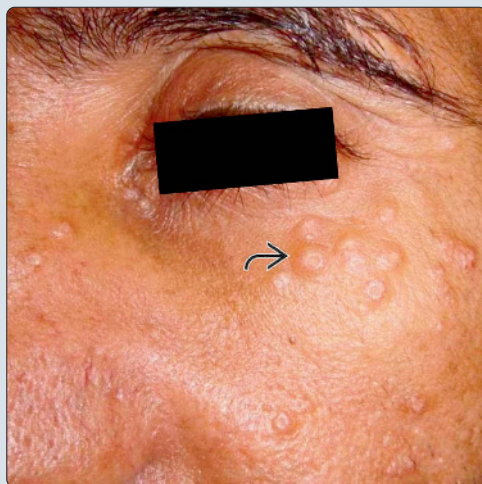
## TOP DIFFERENTIAL DIAGNOSES

- Histoplasmosis
  - 2- to 4- $\mu$ m yeasts often numerous within macrophages with pseudocapsule (mucicarmine negative)
- Lobomycosis
  - Thick-walled birefringent yeasts in chains of rounded and hyaline cells
- Paracoccidioidomycosis
  - Birefringent roundish cells with multiple narrow neck buds resembling mariner's wheel
- Blastomycosis
  - Thick-walled spores (8-15  $\mu$ m in size) with characteristic broad-based budding in nonimmunocompromised patients

## Molluscum-Like Umbilicated Papules

(Left) Cutaneous cryptococcosis (CC) appears most often in immunosuppressed patients, such as this HIV patient who presented with disseminated disease and molluscum-like umbilicated papules [1]. (Courtesy C. Ramos, MD.)

(Right) CC can have quite a varied clinicomorphologic spectrum. This immunosuppressed patient presented with a rhinophymatous, disfiguring, exophytic, weeping tumor of the nose due to CC. (Courtesy S. Chan, MD.)

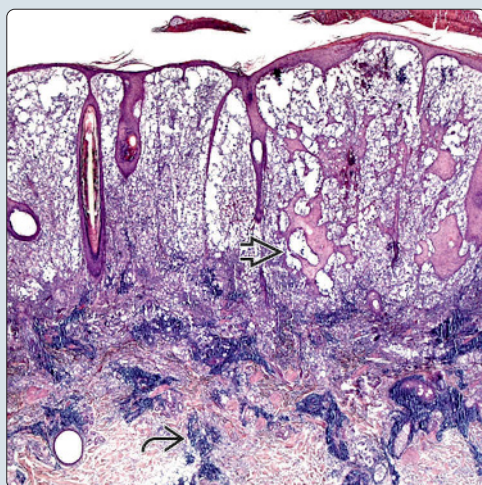


## Exophytic, Weeping Lesion

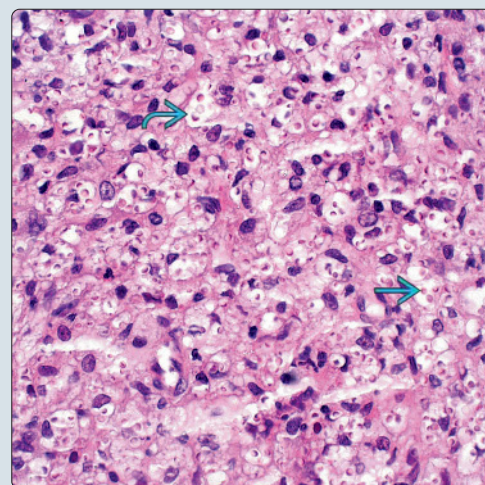


## Pseudoepitheliomatous Hyperplasia and Granulomatous Inflammation

(Left) Low-power view of a case of cryptococcosis demonstrates pseudoepitheliomatous hyperplasia [2] as well as abundant dermal inflammation and dermal granulomatous inflammation [3]. (Right) Higher power view of CC demonstrates numerous yeast-like fungi [4] with a surrounding clear halo [5] indicative of cryptococcosis. (Courtesy S. Billings, MD.)



## Yeast-Like Fungi With Clear Halo





**TERMINOLOGY****Abbreviations**

- Cutaneous cryptococcosis (CC)

**Synonyms**

- Torulosis, Buschke disease, European blastomycosis, crypto

**Definitions**

- Opportunistic infection that most commonly affects lungs and central nervous system
  - Causes substantial morbidity and mortality in immunocompromised patients

**ETIOLOGY/PATHOGENESIS****Infectious Agents**

- 2 species and 4 serotypes recognized
  - *Cryptococcus neoformans* (serotype A and D) and *Cryptococcus gattii* (serotype B and C)
- *C. neoformans* is capsulated spherical yeast measuring 4-20  $\mu\text{m}$  and found in soil, on fruits, and in pigeon droppings and predominantly affects immunocompromised patients
- *C. gattii* has been mostly isolated from decomposing wood in tropical and subtropical areas affecting immunocompetent patients more frequently
- Usually occurs as consequence of hematogenous dissemination of yeasts, after inhalation exposure, or secondary to skin injury caused by untreated wood

**CLINICAL ISSUES****Site**

- Finger and facial sites are particularly common sites in nonimmunocompromised hosts, resembling sporotrichoid pattern
- Infection localized to trunk and lower extremities; multiple lesions are frequently seen in immunocompromised hosts

**Presentation**

- Occurs most often in immunocompromised patients (leukemic, transplant patients, AIDS patients, or those on immunosuppressives)
- Skin involvement can be primary or secondary
- ~ 15% of patients with systemic dissemination show secondary CC
- Primary CC is rare and distinct entity
- Expanded clinicomorphologic spectrum and lack of pathognomonic skin lesion make diagnosis difficult
- Skin lesions typically appear as pedunculated, dome-shaped papules with umbilicated center known as molluscum-like lesions

**Treatment**

- Limited pulmonary or CC in immunocompetent patients without CNS involvement: Fluconazole, itraconazole
- Disseminated cryptococcosis: Amphotericin B and flucytosine as primary induction therapy followed by fluconazole consolidation therapy

**Prognosis**

- Mortality rate of 80% in 2 years without treatment

**MICROSCOPIC****Histologic Features**

- 2 main histopathological patterns
  - Gelatinous type: Numerous budding yeasts with marked variation in size and shape, in foamy stroma with little or no inflammation
  - Granulomatous type: Fewer, smaller organisms and mixed suppurative granulomatous infiltrate of histiocytes, lymphocytes, and giant cells with varying degrees of necrosis
- Molluscum-like lesions show dome-shaped area made up of acanthotic epidermis with transepidermal and transfollicular elimination of *C. neoformans*
  - Inflammatory cells and necrotic dermal debris, including necrobiotic collagen and fragments of capsular material, are present in dermis
- Plaque lesions show pseudoepitheliomatous hyperplasia

**Cytologic Features**

- *C. neoformans* organisms are round, oval, and crescentic in shape, varying from 1-30  $\mu\text{m}$  in diameter, in extracellular and intracellular locations
  - Characteristic peripheral capsular halo

**ANCILLARY TESTS****Serologic Testing**

- Serum cryptococcal antigen detection commonly used for clinical diagnosis

**Histochemistry**

- Grocott, PAS, and GMS stain capsule of thick-walled yeasts
- Mucicarmine stains capsule red

**DIFFERENTIAL DIAGNOSIS****Histoplasmosis**

- No true capsule (pseudocapsule), 2- to 4- $\mu\text{m}$  yeasts, stains mucicarmine negative, and often numerous within macrophages without as striking of peripheral halo as in crypto

**Lobomycosis**

- Thick-walled yeasts that form long chains of rounded and hyaline cells joined by small tubules and thick, birefringent cell wall

**Paracoccidioidomycosis**

- Roundish cells with double membranes that are birefringent with multiple narrow neck buds resembling mariner's wheel

**Blastomycosis**

- Thick-walled spores (8-15  $\mu\text{m}$  in size) with characteristic broad-based budding in patients that are usually not immunosuppressed (vs. crypto, histo, cocci)

**SELECTED REFERENCES**

1. Jackson NA et al: Primary capsule-deficient cutaneous cryptococcosis in a sporotrichoid pattern in an immunocompetent host. *Cutis*. 96(1):E26-9, 2015
2. Neuville S et al: Primary cutaneous cryptococcosis: a distinct clinical entity. *Clin Infect Dis*. 36(3):337-47, 2003

(Left) CC can also present as ulcerated lesions as shown on the dorsum of the hand in this immunocompetent patient. (Right) This patient with CC demonstrated multiple cutaneous nodules in a sporotrichoid pattern.

Ulcerated Skin Lesions

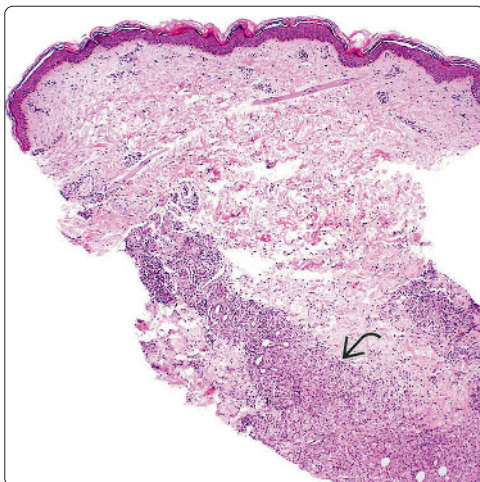


Cutaneous Nodules in Sporotrichoid Pattern

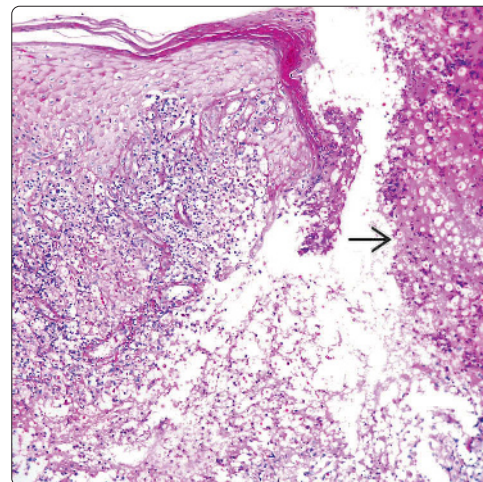


(Left) Low-power view of a skin biopsy of CC demonstrates inflammation located deeper in the dermis and subcutaneous tissue [2]. Organisms were numerous on higher power. (Courtesy S. Billings, MD.) (Right) This biopsy of CC demonstrates pseudoepitheliomatous hyperplasia and transepidermal elimination of the fungus [2].

Deep Dermal Inflammation Extending to Subcutis

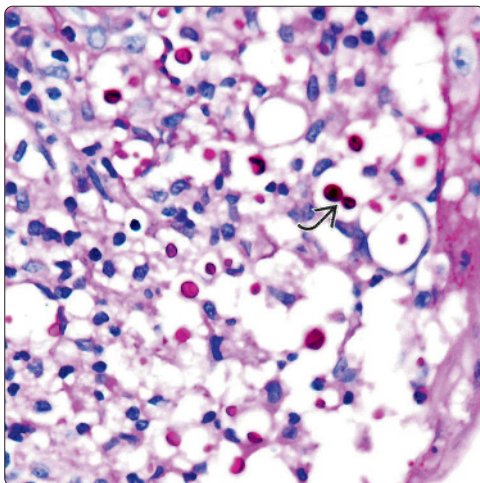


Pseudoepitheliomatous Hyperplasia and Transepidermal Elimination

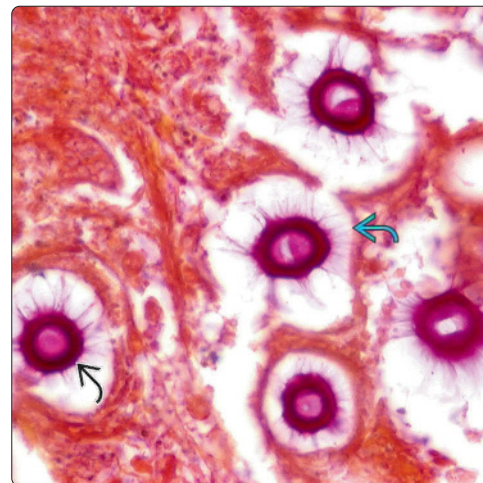


(Left) PAS stain of a case of CC demonstrates characteristic narrow-based budding of cryptococcosis [2]. (Right) High-power view of a case of CC with a mucicarmine highlights the thick, red staining capsule [2] with a peripheral halo [2]. Positive mucicarmine staining of yeast is very helpful in differentiating crypto from other yeast-like fungi. However, it should be kept in mind that capsule-deficient crypto does exist. (Courtesy L. Thompson, MD.)

Narrow-Based Budding on PAS Stain



Red Staining Capsule on Mucicarmine Stain





Polymorphic Clinical Presentation

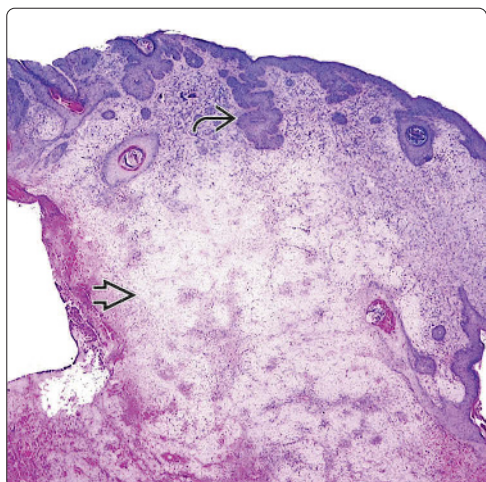


Ulcerated Plaque With Satellite Molluscum-Like Papules

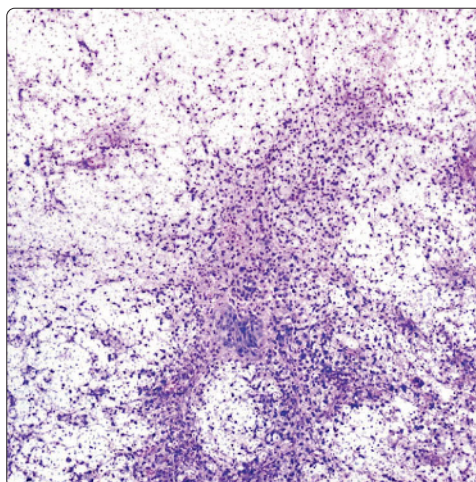


(Left) CC can have a very polymorphic nature as evidenced in this patient with HIV who presented with acneiform papules [A] and pustules [B] and molluscum-like papules [C]. (Courtesy K. Paucar, MD.) (Right) This patient with CC presented with a large ulcerated plaque with multiple satellite molluscum-like papules. (Courtesy K. Paucar, MD.)

Pseudoepitheliomatous Hyperplasia and Myxoid Pattern

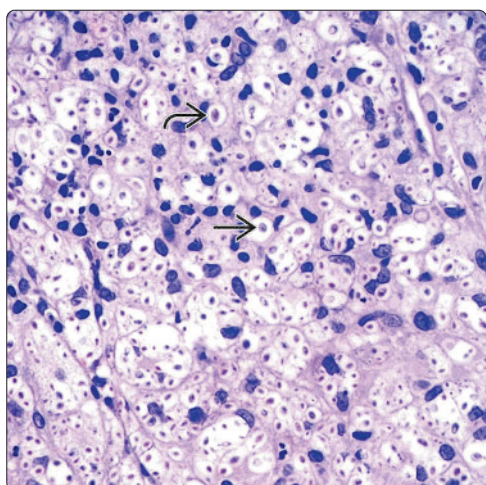


Myxoid Areas With Abundant Organisms

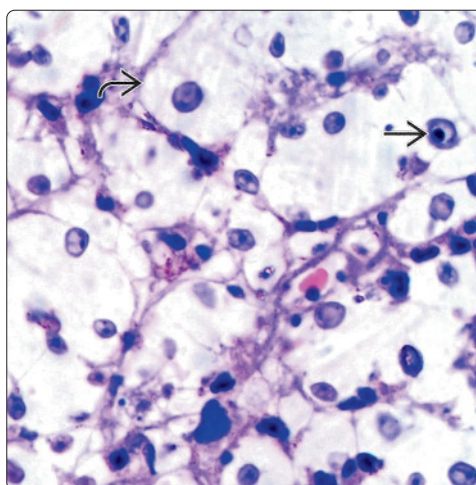


(Left) Low-power view of CC from a plaque-like lesion demonstrates PEH [A] overlying a myxoid pattern of dermal involvement [B]. (Right) Higher power view of a case with dermal myxoid involvement demonstrates a few distinct myxoid areas where the fungus was abundant and the darker areas where the inflammatory infiltrate predominates.

Pleomorphic Organisms with Capsules



Yeasts of Varying Size and Shape



(Left) Higher power view of a case of CC shows multiple pleomorphic microorganisms [A] in various sizes and shapes surrounded by a clear space [B] representing the mucinous capsule. (Right) Higher power view of CC demonstrates numerous yeasts of various shapes, some of them with a prominent nucleolus [A] and surrounding mucinous capsule [B].



# Histoplasmosis

## KEY FACTS

### TERMINOLOGY

- Systemic fungal infection
- In the United States, most commonly caused by yeast *Histoplasma capsulatum*

### CLINICAL ISSUES

- Widely distributed with endemic occurrence in eastern and central United States
  - Especially areas bordering Ohio River Valley and lower Mississippi River
- Skin is usually involved secondarily following primary infection of lung
- Patients with HIV/AIDS have much worse prognosis
- Immunocompetent as well as immunosuppressed persons are affected
- Age groups
  - Affects all ages

### MICROSCOPIC

- Usually caseating or noncaseating granulomatous dermal infiltrate
  - Intracellular 2- to 4- $\mu$ m yeasts surrounded by clear space (pseudocapsule) within macrophages
  - Positive GMS or PAS stains
- Langerhans cells, plasma cells, and lymphocytes predominate infiltrate

### TOP DIFFERENTIAL DIAGNOSES

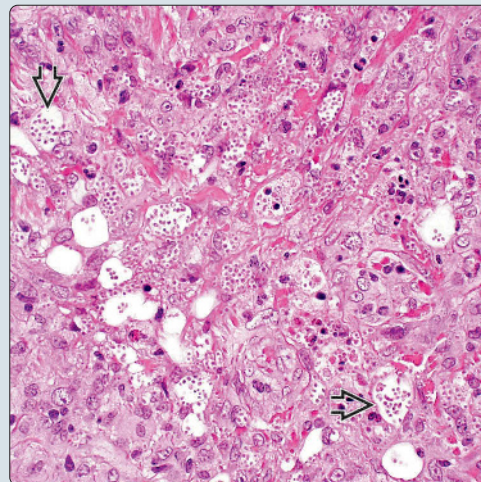
- Leishmaniasis
- Penicilliosis
- Hyalohyphomycosis
- Granuloma inguinale
- Rhinoscleroma
- Cryptococcosis
- Blastomycosis
- Molluscum contagiosum (especially in AIDS patients)

(Left) Histoplasmosis of the tongue presented as a punched-out ulcer in this patient. (Courtesy L. Thompson, MD.) (Right) A biopsy of histoplasmosis of the skin demonstrates numerous yeasts surrounded by a clear halo (pseudocapsule) within macrophages. (Courtesy S. Billings, MD.)

Ulcerated Tongue Lesion

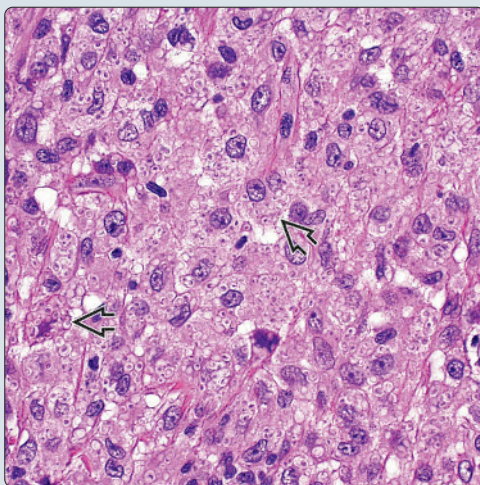


Histoplasmosis Surrounded by Clear Halo

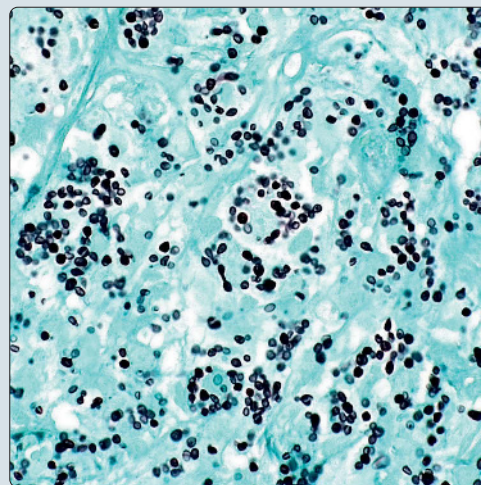


(Left) A higher power view of cutaneous histoplasmosis demonstrates innumerable intracellular yeasts within macrophages. (Courtesy S. Billings, MD.) (Right) A GMS stain is probably the best stain for highlighting the capsule of histoplasmosis, although PAS can also be used. (Courtesy S. Billings, MD.)

Intracellular Yeasts



Silver Stain Highlights Capsule





## TERMINOLOGY

### Synonyms

- Darling disease
- Histo

### Definitions

- Systemic fungal infection
- In United States, most commonly caused by yeast *Histoplasma capsulatum*

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- Exposure to soil contaminated with bird and bat droppings

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Widely distributed with endemic occurrence in eastern and central United States
    - Especially areas bordering Ohio River Valley and lower Mississippi River
  - Immunocompetent as well as immunosuppressed persons are affected
- Age
  - Affects all ages
    - More prone to affect elderly patients with decreased immune systems
- Sex
  - No gender predilection

### Presentation

- Disseminated disease can involve liver, adrenal gland, reticuloendothelial system, meninges, skin, and mucous membranes
- Skin is usually involved secondarily following primary infection of lung
- Rarely, primary cutaneous infections due to traumas are observed
- Cutaneous findings are not specific with papules, nodules, plaques, and punched-out ulcers
- Subclinical findings associated with positive histoplasmin skin test are possible as well

### Laboratory Tests

- Serological testing, urinary antigen testing, cultures, and histologic examination of affected tissue if possible

### Treatment

- Therapy with systemic antifungals is 1st line

### Prognosis

- Patients with HIV/AIDS have much worse prognosis

## MICROSCOPIC

### Histologic Features

- Usually tuberculoid, caseating or noncaseating granulomatous dermal infiltrate with intracellular 2- to 4-µm yeasts surrounded by clear space (pseudocapsule) within macrophages

- Causative pathogen can be highlighted with silver (i.e., GMS) or PAS stains
- Langerhans cells, plasma cells, and lymphocytes predominate infiltrate
- Old lesions show fibrosis in variable degree
- Lesions in AIDS patients may show very mild inflammatory infiltrate

## DIFFERENTIAL DIAGNOSIS

### Histopathological

- Leishmaniasis
  - Most important histologic differential diagnosis (similar-sized organisms within histiocytes)
  - Nucleus and kinetoplast in leishmaniasis (latter often hard to identify)
  - Different geographical distribution (not found in central or eastern United States)
- Hyalohyphomycosis
  - Includes numerous, often opportunistic, infectious organisms that are usually nonpigmented and septate on histology
    - *Penicillium* is toughest to differentiate from histoplasmosis histologically but reproduces by schizogony and not budding
      - Septations can often be seen within yeast of *Penicillium*, especially with help of special stains
  - Culture often necessary to definitively determine causative organism
- Granuloma inguinale
  - Large, parasitized macrophages (~ 20 µm)
  - Silver staining demonstrates intracytoplasmic, bipolar-staining "Donovan bodies" either in clusters or singly
- Rhinoscleroma
  - Large foamy macrophages (Mikulicz cells) filled with gram-negative intracytoplasmic bacilli
  - Not endemic in United States (found in Central and South America, Europe, Middle East, Asia, and Central Africa)
- Cryptococcosis
  - Dermal granulomatous inflammation
  - Yeast with positive mucicarmine or Alcian blue capsule within macrophages and free within tissue
- Blastomycosis
  - Typically shows pseudoepitheliomatous hyperplasia (vs. histoplasmosis)
  - Characteristic broad-based budding yeast that also stain with PAS or GMS

### Clinical

- Molluscum contagiosum (especially in AIDS patients)
  - More rapid in onset (vs. histoplasmosis)
  - Biopsy necessary to differentiate
- Cryptococcus neoformans (especially in AIDS patients)
  - Biopsy, culture, or smear necessary to differentiate

## SELECTED REFERENCES

1. Soza GM et al: Disseminated cutaneous histoplasmosis in newly diagnosed HIV. *Proc (Bayl Univ Med Cent)*. 29(1):50-1, 2016
2. Sun NZ et al: Cutaneous histoplasmosis in renal transplant recipients. *Clin Transplant*. 28(10):1069-74, 2014

## Blastomycosis

## KEY FACTS

## ETIOLOGY/PATHOGENESIS

- Exposure to thermally dimorphic fungus  
*Blastomyces dermatitidis* found naturally in soil

## CLINICAL ISSUES

- 2 classic cutaneous presentations
  - Verrucous: Plaque with atrophic cribriform center and pustules at periphery
  - Ulcerative: Pustule that rapidly progresses to ulcer with heaped-up borders

## MICROSCOPIC

- Verrucous form
  - Papillomatous with pseudoepitheliomatous hyperplasia and often overlying crust
  - Dermal microabscesses (clue: Look for infectious organisms on higher power)
- Ulcerative form
  - Dermal microabscesses histologically  $\pm$  exudative base

- Both forms demonstrate thick-walled spores (8-15  $\mu$ m in size), often within giant cells or free in tissue with
  - Characteristic broad-based budding of spores
- Both demonstrate acute and chronic diffuse inflammatory infiltrate
  - Neutrophils predominate (forming microabscesses) along with lymphocytes, histiocytes (sometimes forming noncaseating granulomas), plasma cells, and multinucleated foreign body type giant cells

## TOP DIFFERENTIAL DIAGNOSES

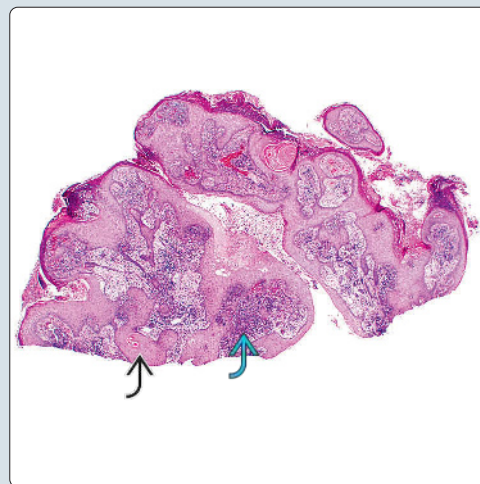
- Other cutaneous fungal infections with pseudoepitheliomatous hyperplasia
  - Histoplasmosis
  - Coccidioidomycosis
  - Chromomycosis
  - Culture is gold standard
- Well-differentiated squamous cell carcinoma

**Large Ulcerated Lesion of Cutaneous Blastomycosis Mimicking Carcinoma**

(Left) Cutaneous blastomycosis often mimics malignancy, especially squamous cell carcinoma. This large, ulcerated lesion shows classic heaped-up borders. (Courtesy S. Moschella, MD.) (Right) Low-power view of verrucous blastomycosis reveals significant PEH [A] of the epidermis that can mimic squamous cell carcinoma. On higher power, amidst dermal inflammation [B], fungal organisms were evident.

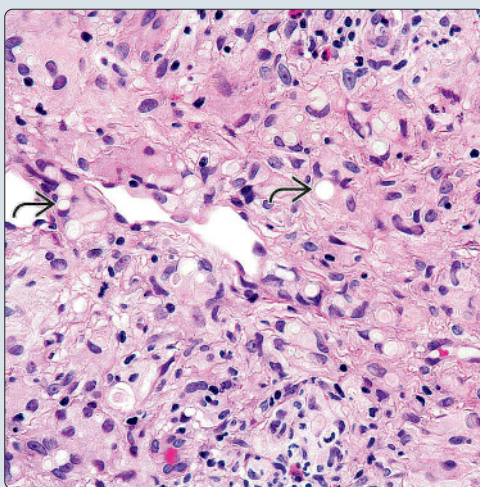


**Pseudoepitheliomatous Hyperplasia in Cutaneous Blastomycosis**

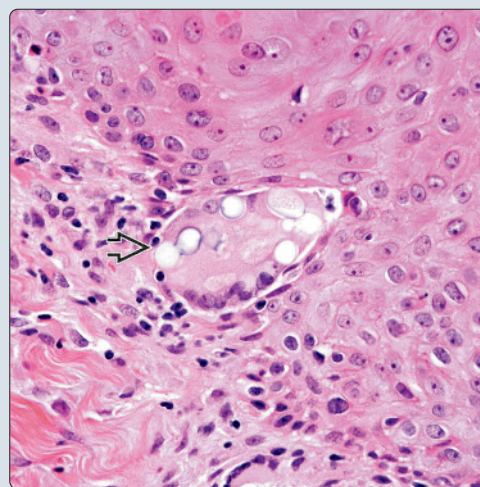


**Numerous Thick-Walled Fungal Organisms Within Histiocytes and Giant Cells**

(Left) Higher power view of a case of blastomycosis demonstrates multiple thick-walled fungal organisms [A] within histiocytes, giant cells, and free in tissue. (Right) High-power view of blastomycosis demonstrates several fungal organisms within a giant cell with evidence of broad-based budding [B]. Other fungal organisms can at times appear identical. Culture is often necessary to definitively identify the causative fungus.



**Fungal Organisms Within Giant Cell With Broad-Based Budding**





## TERMINOLOGY

### Synonyms

- Blasto, Gilchrist disease, North American blastomycosis, Chicago disease

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- Exposure to thermally dimorphic fungus *Blastomyces dermatitidis* found naturally in soil of
  - Ohio River and Mississippi River deltas, Great Lakes area of USA, and St. Lawrence Riverway
  - Most North American cases in south central or southeastern USA
- Unlike most other fungal pathogens, not more common in immunocompromised

## CLINICAL ISSUES

### Epidemiology

- Age
  - Affects all ages
- Sex
  - Men more commonly affected than women and children
    - Due more to propensity to work outdoors and engage in outdoor recreational activities than to susceptibility

### Presentation

- Called great masquerader because of variable pulmonary and cutaneous presentations that often mimic cancer
  - In skin, mimics basal cell and squamous cell carcinoma (SCC)
- After lung, skin is 2nd most common site
  - Cutaneous lesions also noted in 40-80% of disseminated cases
- 2 classic cutaneous presentations
  - Verrucous: Plaque with atrophic cribriform center and pustules at periphery
  - Ulcerative: Pustule that rapidly progresses to ulcer with heaped-up borders
    - Rare purely pustular variant reported

## MICROSCOPIC

### Histologic Features

- Verrucous form
  - Papillomatous with pseudoepitheliomatous hyperplasia and often overlying crust
  - Dermal microabscesses (clue: Look for infectious organisms on higher power)
- Ulcerative form
  - Dermal microabscesses histologically ± exudative base
- Both forms demonstrate thick-walled spores (8-15 µm in size), often within giant cells or free in tissue with
  - Characteristic broad-based budding of spores
  - GMS stain makes organisms more easily appreciable
- Both demonstrate acute and chronic diffuse inflammatory infiltrate

- Neutrophils predominate (forming microabscesses) along with lymphocytes, histiocytes (sometime forming noncaseating granulomas), plasma cells, and multinucleated foreign body type giant cells

## ANCILLARY TESTS

### Special Stains

- GMS or PAS stain may be used to help highlight spores and identify broad-based budding
  - However, spores are often easily visible on routine H&E

### Culture

- Fungal culture is best way to diagnose

### Serology/Skin Tests

- Not helpful for diagnosis

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Other infectious skin diseases or conditions that cause pseudoepitheliomatous hyperplasia (PEH) histologically
  - Infectious causes include: Alternariosis, histoplasmosis, sporotrichosis, coccidioidomycosis, chromomycosis, paracoccidioidomycosis, cat scratch disease, lupus vulgaris, granuloma inguinale, and others
    - Identification of responsible organisms by careful searching on high power or through use of special stains clinches diagnosis
    - Culture is gold standard, especially when no organisms seen or definitive organism identification on histologic grounds is not possible
  - Noninfectious causes include stasis dermatitis and pyoderma gangrenosum
- SCC, well differentiated
  - Blastomycosis in particular can cause marked PEH reaction that may mimic SCC
  - SCC should have some degree of cytologic atypia, nuclear polymorphism, dysmaturation, or mitoses
    - May be some reactive atypia in blasto
  - PEH of blasto typically has tongue-like projections of squamous epithelium
    - Border of SCC more pushing or frankly infiltrative

### Clinical

- SCC
  - More apt to be painful, have indurated edge, and usually on sun-exposed skin
- Other fungal infections
  - Generally indistinguishable clinically
- Furuncle, carbuncle, or ruptured sebaceous cyst
  - Recent in onset, fluctuant lesions

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2. Ortega-Loayza AG et al: Images in clinical medicine. Cutaneous blastomycosis. *N Engl J Med*. 368(10):e13, 2013
3. Saccente M et al: Clinical and laboratory update on blastomycosis. *Clin Microbiol Rev*. 23(2):367-81, 2010
4. Mason AR et al: Cutaneous blastomycosis: a diagnostic challenge. *Int J Dermatol*. 47(8):824-30, 2008

## Chromomycosis

## KEY FACTS

## TERMINOLOGY

- Chronic cutaneous and subcutaneous fungal infection due to dematiaceous (pigmented) fungi

## CLINICAL ISSUES

- Most commonly reported in tropical and subtropical regions in outdoor workers with poor protective footwear or clothing
- Chronic lesions develop polymorphous presentation including
  - Plaques, verrucous, nodular, or tumorous lesions

## MICROSCOPIC

- Tissue response is nonspecific and often mimics other deep mycoses
- Hyperkeratosis and pseudoepitheliomatous hyperplasia (PEH) often

- Dermal mixed acute and chronic inflammation with microabscesses, granulomatous inflammation, and giant cells are typical
  - Pigmented fungal elements may or may not be present amidst dermal inflammation
    - Hallmark is identification of medlar bodies (pigmented fungi) amidst inflammation singly, in chains, or clusters

## TOP DIFFERENTIAL DIAGNOSES

- Phaeohyphomycosis
  - More commonly affects immunocompromised patients but also affects immunocompetent patients
  - Forms pigmented hyphae, pseudohyphae, or yeast-like cells vs. pigmented yeast of chromomycosis
- Mycetoma
  - Typically, no PEH with characteristic grains instead of medlar bodies

Verrucous Plaque on Thumb

(Left) Older clinical lesion of chromomycosis presents as a large verrucous plaque on the thumb. Although legs and feet are most common, the disease can affect any cutaneous site. (Courtesy Brooke Army Medical Center teaching file.) (Right) Chromomycosis in this case shows diffuse dermal granulomatous inflammation [E] and a parakeratotic crust [E]. Pseudoepitheliomatous hyperplasia [E] is often present.

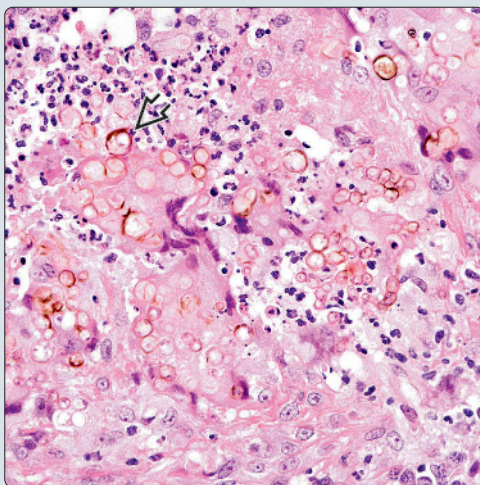


Pseudoepitheliomatous Hyperplasia With Granulomatous Inflammation

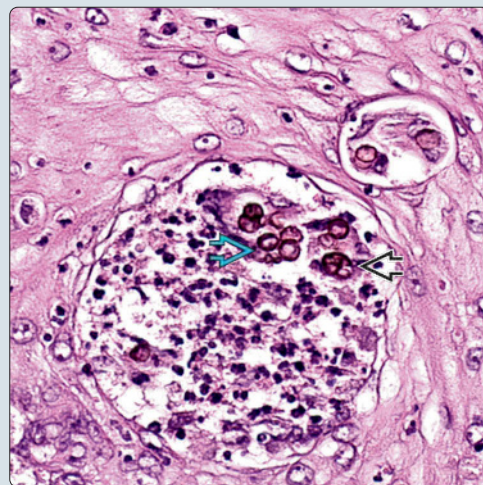


Numerous Medlar Bodies Within Giant Cells

(Left) In the middle of a distinct, large dermal granulomatous nodule, characteristic medlar bodies or copper pennies [E] are identified, solidifying a diagnosis of chromomycosis. (Right) Chromomycosis on histology shows characteristic pigmented yeasts resembling copper pennies often singly, in pairs, triads [E], or tetrads [E], and often amidst surrounding pseudoepitheliomatous hyperplasia.



Pigmented Yeasts Resembling Copper Pennies





## TERMINOLOGY

### Synonyms

- Chromoblastomycosis, chromo, cladosporiosis, Fonseca disease, Pedroso and Lane mycosis, phaeosporotrichosis

### Definitions

- Chronic cutaneous and subcutaneous fungal infection due to dematiaceous (pigmented) fungi

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- Several infectious causative agents have been identified to date
  - *Fonsecaea pedrosoi* (most frequent), *Cladosporium* (*Cladophialophora*) *carrionii*, *Phialophora verrucosa*, *Fonsecaea compacta*, and *Rhinocladiella aquaspersa* are 5 most frequent causes
    - Less frequently *Exophiala dermatitidis*, *Exophiala jeanselmei*, *Exophiala spinifera*, *Wangiella dermatitidis*, *Cladosporium arxii*, and *Botryomyces caespitosus*
- Infectious organisms usually gain entry into human tissue via traumatic injury with wood splinter or thorn
  - For this reason, lesions frequently found on feet and legs in outdoor workers from endemic areas

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Typically occurs in immunocompetent patients
    - However, kidney transplant patients or patients on chronic corticosteroids also commonly affected
  - Infected patients 10x more likely have HLA-A29 histocompatibility antigen
- Age
  - Affects all ages, but most often postadolescent adults
- Sex
  - M:F = 5-9:1
- Ethnicity
  - Most commonly reported in tropical and subtropical regions in outdoor workers with poor protective footwear or clothing
    - Brazil, Madagascar, South Africa, and Costa Rica are countries with highest prevalence

### Site

- Limbs (especially feet and legs) most frequent site affected

### Presentation

- Several months after initial inoculation, painless unilateral papules or nodules appear
  - Over weeks papules become scaly
  - Eventually lesions may develop polymorphous presentation including
    - Plaques, verrucous, nodular, or tumorous lesions

### Treatment

- Options, risks, complications
  - Cryotherapy can be used for more verrucous lesions
- Surgical approaches

- For small, localized lesions, surgical excision with wide margins is treatment of choice
- Drugs
  - For deeper or more extensive lesions, combination oral itraconazole and terbinafine is usually used
    - Single agent itraconazole may be used but 18-30 months duration is often needed

### Prognosis

- Generally good with adequate treatment; however, notoriously hard to treat and recurrence is common in partially treated lesions
- Squamous cell carcinoma may rarely develop in chronic lesions or in residual scars

## MICROSCOPIC

### Histologic Features

- Tissue response is nonspecific and often mimics other deep mycoses
- Hyperkeratosis and pseudoepitheliomatous hyperplasia (PEH) often
- Dermal mixed acute and chronic inflammation with microabscesses, granulomatous inflammation, and giant cells are typical
  - Pigmented fungal elements may or may not be present amidst dermal inflammation
  - Hallmark is identification of medlar bodies (pigmented fungi) amidst inflammation singly, in chains, or in clusters

### Cytologic Features

- Identification of pigmented fungi: Medlar bodies (a.k.a. sclerotic, fumagoid, chromo bodies, or muriform cells) is characteristic
  - Muriform cells/medlar bodies resemble copper pennies histologically

## ANCILLARY TESTS

### Culture

- Only way to definitively identify causal species, but not always successful

### KOH Prep

- Skin scrapings may reveal characteristic muriform bodies (cells)

## DIFFERENTIAL DIAGNOSIS

### Phaeohyphomycosis

- More commonly affects immunocompromised patients, but also affects immunocompetent patients
- Forms pigmented hyphae, pseudohyphae, or yeast-like cells vs. pigmented yeast of chromomycosis

### Mycetoma

- Typically no PEH with characteristic grains instead of medlar bodies

## SELECTED REFERENCES

1. Mouchalouat Mde F et al: Chromoblastomycosis: a clinical and molecular study of 18 cases in Rio de Janeiro, Brazil. *Int J Dermatol*. 50(8):981-6, 2011
2. Ameen M: Chromoblastomycosis: clinical presentation and management. *Clin Exp Dermatol*. 34(8):849-54, 2009

## KEY FACTS

## TERMINOLOGY

- Cutaneous fungal infection due to angioinvasive *Aspergillus* spp.

## ETIOLOGY/PATHOGENESIS

- *A. fumigatus*, *A. flavus* most common (70%)
  - Remainder composed of *A. terreus*, and *A. niger*
    - Rarely *A. glaucus*, *A. chevalieri*, or *A. ustus*

## CLINICAL ISSUES

- Key risk factor: Immunocompromise
- Primary cutaneous lesions arise from direct local inoculation/colonization
- Secondary cutaneous lesions arise from hematogenous dissemination usually of sinobronchopulmonary origin

## MICROSCOPIC

- 2- to 4- $\mu$ m septated hyaline hyphae with dichotomous branching at 45° angle

- Angioinvasion, overlying tissue ischemic necrosis and hemorrhage

## TOP DIFFERENTIAL DIAGNOSES

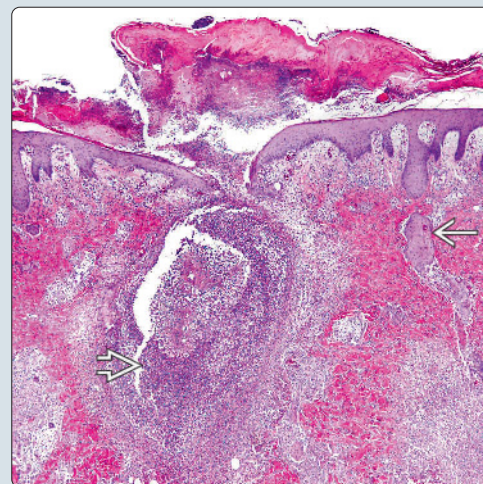
- Fusariosis, hyalohyphomycosis
  - *Fusarium* spp. and *Scedosporium* spp. can morphologically look identical to *Aspergillus*
    - Culture necessary to distinguish
- Ecthyma gangrenosum
  - Clinically, cutaneous findings may be indistinguishable
  - Biopsy should reveal numerous gram-negative bacilli in media and adventitia of vessels
- Zygomycosis/mucormycosis
  - Mucorales are typically nonseptated and broader with 90° branching
- Candidiasis
  - 2- to 4- $\mu$ m thick pseudohyphae with 3- to 6- $\mu$ m oval spores

(Left) Classic cutaneous aspergillosis lesion demonstrates an evolving violaceous nodule with central ulceration and eschar formation. (Right) Low-power view of cutaneous aspergillosis demonstrates abscess formation and ulceration with a background of a mixed inflammatory dermal infiltrate. Pseudoepitheliomatous epidermal hyperplasia is present.

Central Eschar in Aspergillosis Nodule

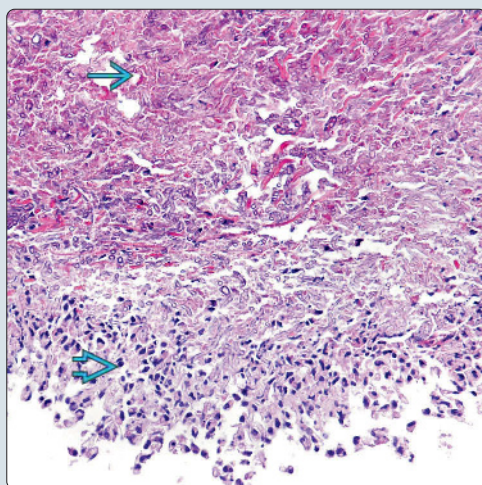


Pseudoepitheliomatous Epidermal Hyperplasia

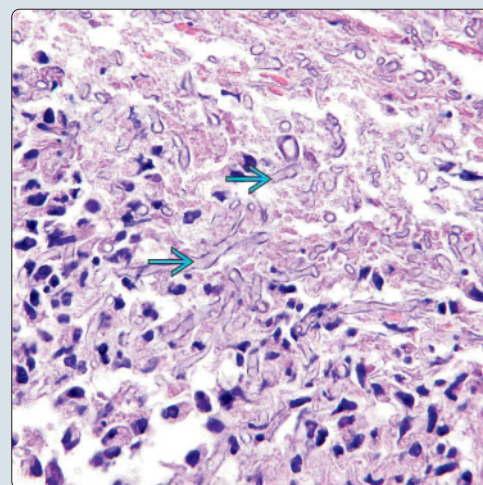


(Left) Large area of necrosis with admixed hyphae and surrounding inflammatory infiltrate is shown. (Right) High-power image demonstrates hyphae within necrotic background.

Necrotic Debris



Hyphae Within Necrotic Debris





## TERMINOLOGY

### Definitions

- Cutaneous fungal infection due to angioinvasive *Aspergillus* spp.
- Primary cutaneous lesions arise from direct local inoculation/colonization
  - Host is most often immunocompromised or, rarely, immunocompetent
- Secondary cutaneous lesions arise from hematogenous dissemination, usually of sinobronchopulmonary origin, in immunocompromised host

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- Ubiquitous soil- and water-dwelling fungal organism
- Contact made through direct inhalation of spores (conidia) or primary inoculation of skin
- Hospital renovations or construction may increase ambient spore count

### Infectious Agents

- *Aspergillus fumigatus*, *Aspergillus flavus* most common (70%)
- Remainder composed of *Aspergillus terreus*, and *Aspergillus niger*
  - Rarely *Aspergillus glaucus*, *Aspergillus chevalieri*, or *Aspergillus ustus*

### Pathogenesis

- Angioinvasion through binding to vessel wall components leading to thrombosis, ischemia, and infarction of surrounding tissue
- Facilitated by release of toxins, proteases, secondary metabolites, and inhibition of NADPH oxidase activation in leukocytes

### Risk Factors

- Immunosuppression or immunocompromise
  - Hematological malignancies, chemotherapy, chronic steroids or antibiotics
  - Bone marrow or solid organ transplantation
  - HIV and chronic granulomatous disease
    - At risk for invasive infection when CD4 count < 50 mm<sup>3</sup>
  - Primary infection is rare, usually due to occlusive tape

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - 2nd most common opportunistic fungal infection after *Candida*
    - Accounts for 20% of fungal infections in bone marrow or solid organ transplant patients
    - May occur in up to 5% of acute leukemia patients
  - Cutaneous lesions occur in 5-11% of patients with documented *Aspergillus* infection
  - Primary cutaneous lesions more common in burn victims, neonates, and solid organ transplants
  - Secondary cutaneous lesions more common in bone marrow transplant recipients

- Equal distribution of primary/secondary lesions in leukemia

- Age
  - Can affect patients of any age, including neonates

### Site

- **Primary cutaneous lesions**
  - Occur at sites of skin trauma
    - IV catheter sites, wounds, burns, surgical sites, occlusive tape/dressings
  - In immunocompetent hosts may be associated with agricultural trauma
- **Secondary cutaneous lesions**
  - Primary infection is usually of bronchopulmonary origin, although may also invade and disseminate from nasal sinuses or primary skin lesion
  - Can hematogenously disseminate or spread contiguously to any organ including skin, brain, eyes, kidneys, heart, GI tract, thyroid, bone, & liver

### Presentation

- **Cutaneous findings**
  - Single or multiple erythematous to violaceous papules, plaques, or hemorrhagic bullae that progress to central necrotic ulceration and eschar
    - May also present as subcutaneous granulomas, abscesses, pustular lesions, or vegetating plaques
    - No anatomical site predilection in secondary cutaneous lesions
  - In HIV lesions, may resemble umbilicated papules of molluscum contagiosum
- **Signs/symptoms**
  - Patient is usually febrile, with mild sepsis-like findings and nonspecific laboratory abnormalities
    - Chest pain, dyspnea, and hemoptysis if pulmonary involvement
- **Other organ manifestations**
  - Respiratory tract
    - Invasive sinusitis, ulcerative tracheobronchitis, acute or chronic necrotizing pneumonitis, aspergilloma, allergic bronchopulmonary aspergillosis
  - Heart
    - Endocarditis, pericarditis
  - Brain
    - Single or multiple cerebral abscesses, meningitis, mycotic aneurysm, cerebral granuloma
  - Eyes
    - Endophthalmitis, corneal infection, keratitis

### Treatment

- **Drugs**
  - Acute infection
    - Voriconazole (1st choice)
    - Secondary options: Amphotericin B, caspofungin, posaconazole, micafungin
  - Prophylaxis
    - Posaconazole, itraconazole solution, micafungin, aerosolized amphotericin B
- **Surgical approaches**
  - Debridement and excision in event of primary cutaneous lesion has been reported, but patients are often not surgical candidates

## Prognosis

- Mortality of 75-90% in disseminated infection

## MICROSCOPIC

### Histologic Features

- 2- to 4- $\mu$ m septated hyaline hyphae with dichotomous branching at 45° angle
  - Best visualized with combination of H&E and silver methenamine or PAS
  - Spores/yeast forms are absent
  - Fruiting bodies are rare but confirmatory
- Progression across tissue planes with angioinvasion, overlying tissue ischemic necrosis and hemorrhage
- Inflammatory reaction is nonspecific or absent, although eosinophils may be numerous
- Epidermis may exhibit pseudoepitheliomatous epidermal hyperplasia
- Primary lesions in immunocompetent hosts demonstrate few hyphae with well-developed granulomatous reaction, or suppurative with abscess formation

## ANCILLARY TESTS

### Serologic Testing

- Galactomannan enzyme immunoassay
  - Low sensitivity but good specificity, may have future role as screening tool
  - Utility best established in patients with hematologic malignancy
- $\beta$ -d-glucan
  - Detects cell wall components but is not specific to *Aspergillus* spp.

### Tissue Culture

- Essential for diagnosis, along with tissue biopsy
- Relatively fast-growing and often visible within 1-3 days
- Absence of culture results or definitive histopathologic diagnosis should not delay treatment

### Tissue Biopsy

- Biopsy should be taken from center of lesion with sufficient depth to reach subcutaneous fat

### Noninvasive Modalities

- Sputum/bronchoalveolar lavage
  - False-positives due to pervasive nature of organism

## DIFFERENTIAL DIAGNOSIS

### Fusariosis, Hyalohyphomycosis

- *Fusarium* spp. and *Scedosporium* spp. can morphologically look identical to *Aspergillus*
  - Culture necessary to distinguish

### Ecthyma Gangrenosum

- Clinically, cutaneous findings may be indistinguishable
- Biopsy should reveal numerous gram-negative bacilli in media and adventitia of vessels

### Zygomycosis/Mucormycosis

- Mucorales are typically nonseptated and broader with 90° branching

## Candidiasis

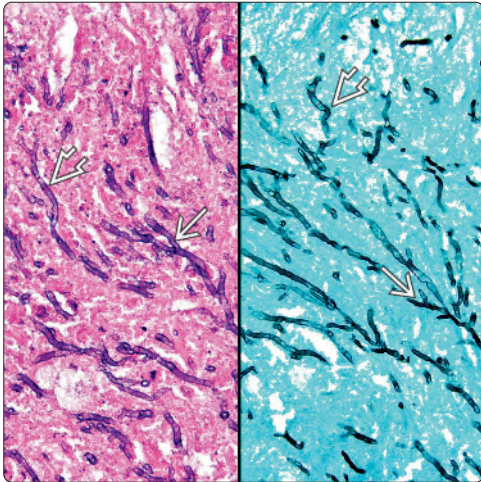
- 2- to 4- $\mu$ m thick pseudohyphae with 3- to 6- $\mu$ m oval spores
  - Budding may or may not be present
    - May only be visible with PAS or GMS

## SELECTED REFERENCES

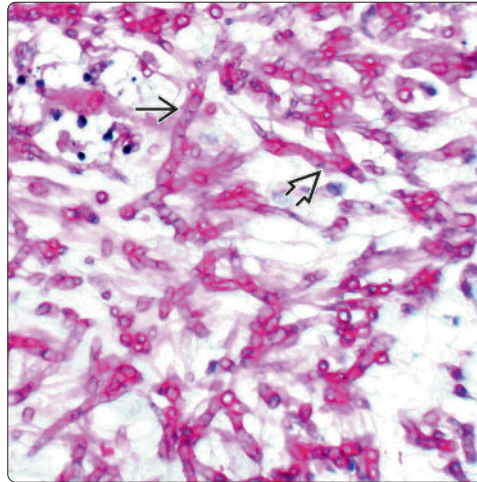
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**H&E and GMS Highlighting Hyphae**

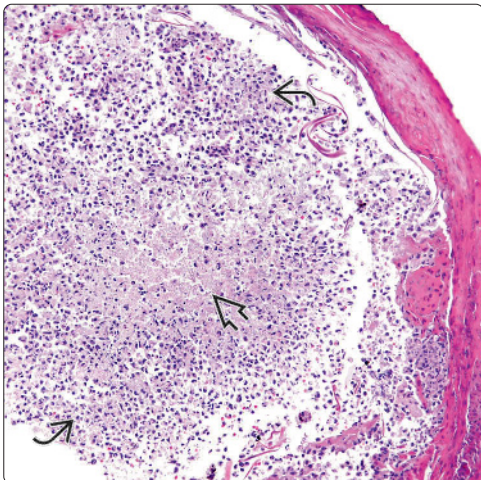


**PAS Highlighting 45° Branching**

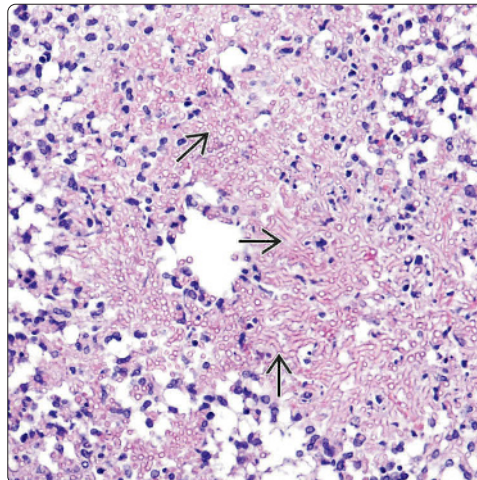


(Left) H&E (left) and GMS (right) stains of cutaneous aspergillosis demonstrate numerous septated fungal hyphae with dichotomous 45° angle branching. (Courtesy L. Thompson, MD.) (Right) Higher power view of cutaneous aspergillosis using a PAS stain demonstrates septated fungal hyphae with arborizing 45° angle branching. (Courtesy D. Cassarino, MD, PhD.)

**Intense Neutrophilic Infiltrate**

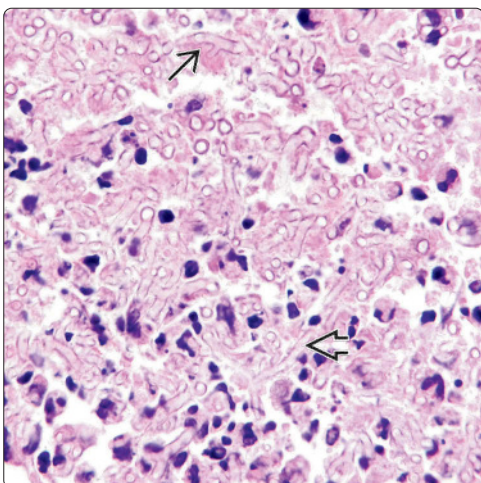


**Numerous Hyphae**

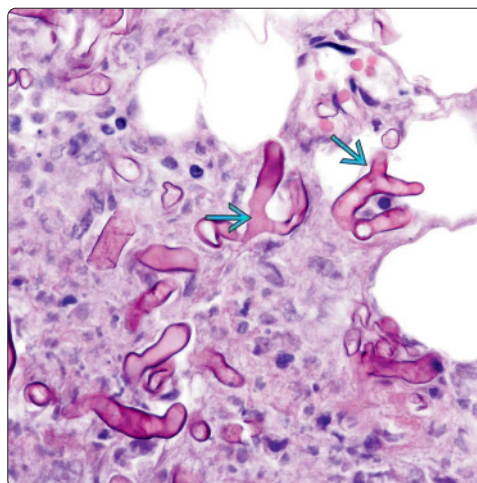


(Left) Numerous neutrophils are surrounding fungal organisms in an immunocompetent patient. Immunocompromised patients may have very mild to no inflammatory response. (Right) Collection of numerous refractile hyphae is shown within an H&E section.

**More 45° Branching**



**Zygomycosis With Broad Ribbons and Aseptate Hyphae**



(Left) High-power view demonstrates numerous hyaline hyphae with 45° branching and a neutrophilic infiltrate. (Right) Cutaneous zygomycosis can appear similar, but it demonstrates broad ribbons with dichotomous 90° angle branching. Hyphae are typically aseptate.



## KEY FACTS

## TERMINOLOGY

- Deep fungal infection caused by 2 orders (Mucorales, Entomophthorales)

## CLINICAL ISSUES

- Mucormycosis
  - 3 forms
  - Cutaneous form with red papules or nodules that progress to vesiculobullous necrosis
  - Rhinosinusitis with invasion of nose, orbit, and eventually intracranial tissue
  - Disseminated in lungs or gastrointestinal tract
  - Prognosis
    - 50% or higher death rate even with early aggressive therapy
    - Also blindness, pulmonary embolus, stroke, and nerve damage


## MICROSCOPIC

- Mucormycosis
  - Rarely septate, predominantly aseptate large, broad, ribbon-like hyphae with characteristic right angle branching
  - Granulomatous tissue reaction surrounding hyphae
  - Sparse dermal inflammation or neutrophilic abscesses
  - Often thrombi, tissue necrosis, and angioinvasion
- Entomophthoromycosis
  - Dermal and subcutaneous infiltrate with numerous eosinophils amid granulomatous inflammation and giant cells

## TOP DIFFERENTIAL DIAGNOSES

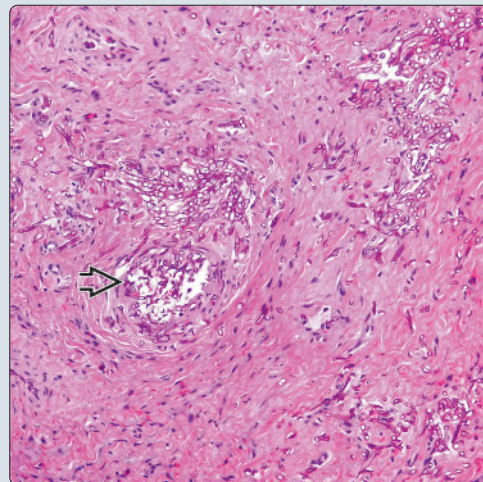
- Aspergillosis
- Fusarium
- Other deep fungal skin infections

Purpuric Abscess


(Left) Undermining granulomatous purpuric abscess over the dorsal hand of a patient with zygomycosis is seen on biopsy. The patient had a heart transplant 2 years prior. (Right) This case of rhinonasal zygomycosis demonstrates the propensity for angioinvasion of this fungal species . Tissue culture would be necessary to confirm correct fungal organisms and rule out aspergillosis.

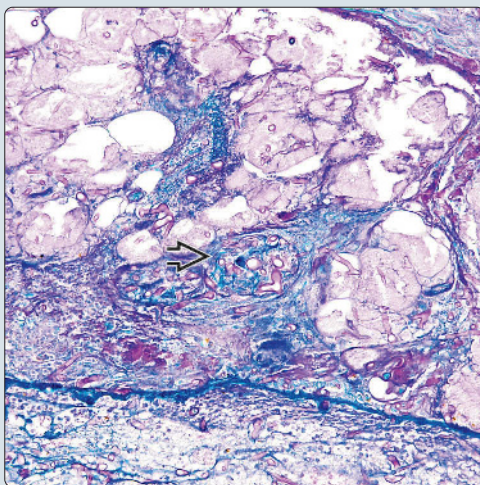


Hollow Tubules Demonstrating Angioinvasion

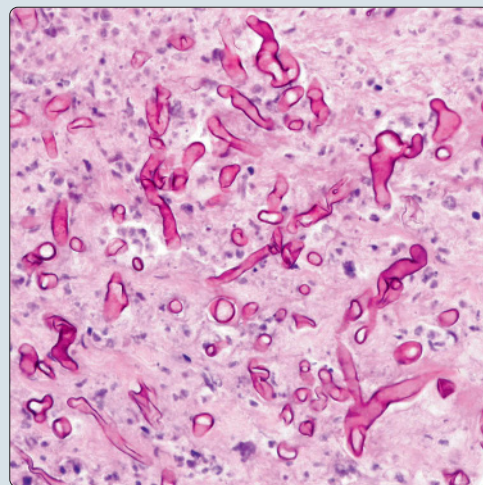


Angiotropic Fungi With Right Angle Branching

(Left) PAS stain shows angiotropic propensity for zygomycosis to invade vessels  and the thick, hollow outlines of the fungus. (Right) Characteristic morphology of zygomycosis in a skin biopsy shows broad, aseptate, ribbon-like hollow hyphae with right angle branching sometimes resembling moose antlers. Culture would be necessary to rule out aspergillosis, which can have similar morphology (typically septate & acute angle branching).



Broad, Aseptate Ribbons With Right Angle Branching





## TERMINOLOGY

### Synonyms

- Mucormycosis, entomophthoromycosis (rhinophycomycosis), phycomycosis, basidiobolomycosis

### Definitions

- Deep fungal infection affecting immunocompromised (order Mucorales) or immunocompetent (order Entomophthorales) patients

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- Zygomycota phylum contains Mucorales and Entomophthorales orders
  - Family Mucoraceae: *Absidia*, *Apophysomyces*, *Mucor*, *Rhizomucor*, and *Rhizopus* spp.
    - Primarily affects immunocompromised (esp. ketoacidotic diabetics)
    - Also affects transplant patients, leukemia patients; systemic corticosteroids, GVHD, deferoxamine, contaminated bandages, HIV
    - Any condition that causes neutropenia
  - Entomophthorales order includes *Basidiobolus* and *Conidiobolus* spp.
    - Causes chronic subcutaneous disease in immunocompetent patients
    - Geographically confined mainly to tropical regions of South America, Africa, and Asia

## CLINICAL ISSUES

### Presentation

- Mucormycosis
  - Much more common than entomophthoromycosis
  - 3 forms
    - Cutaneous form with red papules or nodules that progress to vesiculobullous necrosis
    - Rhinosinusitis with invasion of nose, orbit, and eventually intracranial tissue
    - Disseminated in lungs or gastrointestinal tract
- Entomophthoromycosis (basidiobolomycosis, conidiobolomycosis)
  - 3 forms
    - Subcutaneous with deep tracts into bone, underlying structure, or blood dissemination
    - Centrofacial with nasal obstruction, rhinitis, and epistaxis
    - Visceral (very rare)

### Treatment

- Mucormycosis
  - Aggressive surgical debridement is essential
  - Liposomal amphotericin B; if this fails, then posaconazole
- Entomophthoromycosis
  - Aggressive surgical debridement is essential
  - Potassium iodide, then liposomal amphotericin B, then itraconazole

### Prognosis

- Mucormycosis

- 50% or higher death rate even with early aggressive therapy
  - Also blindness, pulmonary embolus, stroke, and nerve damage
- Entomophthoromycosis
  - At least 50% mortality even with early aggressive therapy

## MICROSCOPIC

### Histologic Features

- Mucormycosis
  - Rarely septate (often not recognized in books and literature), but predominantly aseptate large, broad hyphae with characteristic right angle branching
  - Ulceration often present
  - Granulomatous tissue reaction surrounding hyphae
  - Sparse dermal inflammation or neutrophilic abscesses
  - Often thrombi, tissue necrosis, and angioinvasion
- Entomophthoromycosis
  - Dermal and subcutaneous infiltrate with numerous eosinophils amid granulomatous inflammation and giant cells
    - Fungal hyphae (4-10 µm in diameter) within giant cells and free-floating amidst inflammation for *Conidiobolus* spp.
    - Fungal septate hyphae with branching (7-15 µm) within granulomas for *Basidiobolus* spp.

## DIFFERENTIAL DIAGNOSIS

### Histological

- Aspergillosis
  - Most important differential diagnosis
  - Hyphae are septate and demonstrate characteristic acute angle branching
    - Zygomycosis can rarely show septate hyphae
  - Tissue culture often required for true species identification
- Fusarium
  - Acute branching septate hyphae similar to *Aspergillus*
  - Much rarer than *Aspergillus*, limited to immunosuppressed patients (especially leukemic patients with advanced neutropenia)
  - Can be localized or disseminated disease in skin
- Other deep fungal infections
  - Chromomycosis, coccidioidomycosis, paracoccidioidomycosis, alternariosis, histoplasmosis, sporotrichosis, others
    - Most have pseudoepitheliomatous hyperplasia and granulomatous inflammation with distinctive organismal morphology

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## Mycetoma

## KEY FACTS

## TERMINOLOGY

- Localized chronic granulomatous infection involving skin, subcutaneous tissue, and occasionally underlying soft tissue and bone; can be caused by either fungi or bacteria

## CLINICAL ISSUES

- Classic clinical triad of draining sinuses, swollen tissues, and identifiable grains in discharge are classic

## MICROSCOPIC

- Type 1 reaction: Grains surrounded by layer of neutrophils, then layer of chronic inflammatory cells, and finally layer of fibrous tissue
- Type 2 reaction: Very similar to type 1 reaction except innermost neutrophil layer is replaced by giant cells and macrophages engulfing grains
- Type 3 reaction: Well-formed epithelioid granulomas, including Langhans giant cells, occasionally with central remnants of fungi

- Eumycetes are filaments wider than 1  $\mu\text{m}$ , often forming mass of hyphae in intercellular cement
- Common to see Splendore-Hoepli phenomenon, which is amorphous, eosinophilic, radially arranged material surrounding mass of hyphae or filamentous bacteria
- Black grains are usually golden brown on H&E staining
- Actinomycete granules are  $\sim 100 \mu\text{m}$  in diameter with fine branched filaments  $\sim 1 \mu\text{m}$  in diameter

## TOP DIFFERENTIAL DIAGNOSES

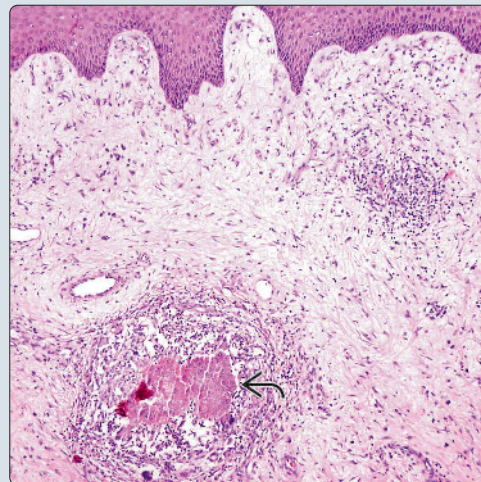
- Botryomycosis (bacterial pseudomycosis)
- Sporotrichosis
- Chromomycosis
- Subcutaneous phaeohyphomycosis
- Hyalohyphomycosis
- Majocchi granuloma

Draining Sinus Tracts

(Left) Mycetoma of the right foot from a patient stationed in Guam demonstrates several draining sinus tracts (present for months) with tissue swelling and slight hyperpigmentation. (Courtesy J. Steger, MD.) (Right) Although usually more deep-seated, characteristic pale grains of eumycetoma are seen surrounded by inflammation. (Courtesy S. Florell, MD.)

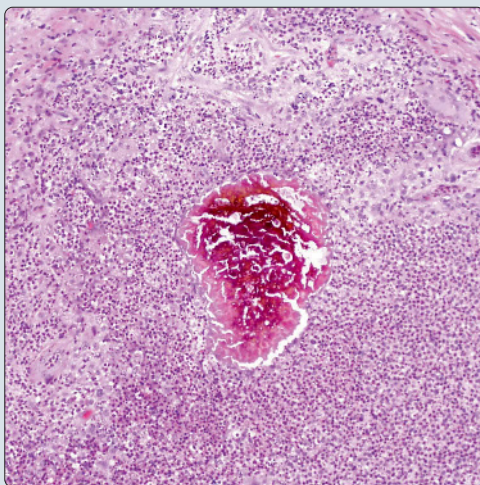


Pale Grains Surrounded by Inflammation

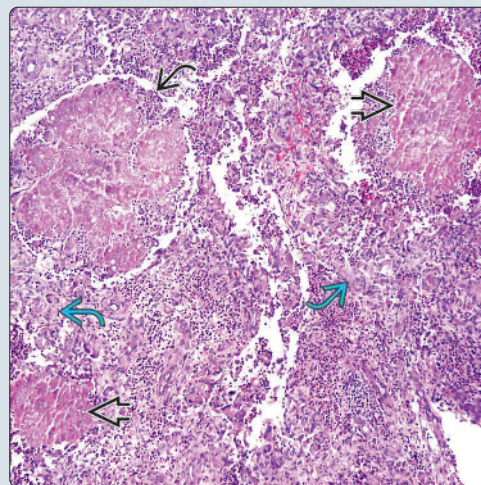


Black Grains (Brown on H&amp;E) Surrounded by Neutrophils

(Left) Black grains of eumycetoma (brown on H&E) are surrounded by numerous neutrophils. (Right) A case of eumycetoma demonstrates numerous pale grains deep in the subcutaneous tissue surrounded by a layer of acute inflammatory cells and then a layer of chronic inflammatory cells.



Pale Grains in Subcutis Surrounded by Inflammation





**TERMINOLOGY****Synonyms**

- Madura foot, maduromycosis

**Definitions**

- Localized chronic granulomatous infection involving skin, subcutaneous tissue, and occasionally underlying soft tissue and bone; can be caused by either fungi or bacteria

**ETIOLOGY/PATHOGENESIS****Infectious Agents**

- Most common causal organisms are either true fungi from class Eumycetes (eumycetomas) or filamentous bacteria from class Actinobacteria (actinomycetomas)
  - In eumycetomas, most common causal agent worldwide is *Madurella mycetomatis*; although, many other species can cause disease
    - In USA, *Pseudallescheria boydii* is most common agent
  - In actinomycetomas, *Nocardia brasiliensis* and *Actinomyadura madurae* are 2 most common isolates

**CLINICAL ISSUES****Epidemiology**

- Incidence
  - Unknown due to slow progression and late presentation in most patients
- Age
  - Most infections occur in patients aged 20-40 years
- Sex
  - M:F ~ 4:1
- Ethnicity
  - Most cases occur in tropical and subtropical populations
  - Mycetoma belt includes areas between latitudes 15° south and 30° north
    - Includes India, Mexico, Venezuela, Colombia, Argentina, Sudan Somalia, and Senegal
  - Occasional case report in USA and Europe
  - People involved with fieldwork &/or frequent contact with soil (herdsmen, farmers, field laborers) are more commonly affected

**Site**

- Feet most common location (~ 70%)
  - Other common sites include hands, legs, knee joints, arms
- Actinomycetomas of shoulder are commonly seen in Mexico, especially in lumber workers carrying logs

**Presentation**

- Classic clinical triad of draining sinuses, swollen tissues, and identifiable grains in discharge are classic
  - Black discharging grains are characteristic of eumycetoma
  - White/yellow-colored grains (pale grains) can be seen in both eumycetoma and actinomycetoma
- 2 common histories
  - Initial pain and discomfort upon inoculation
  - No recollection of any preceding trauma
- After inoculation, painless subcutaneous nodule develops and slowly spreads

- Nodule slowly increases in size, developing draining sinuses and sometimes secondary nodules and papules
- Some sinuses close and heal, while other new ones are formed
- Overlying skin often hyperpigmented, but occasionally hypopigmented
- As lesions continue to develop, subcutaneous abscesses develop and lesions extend to involve underlying soft tissue and bone
  - If left untreated, bone destruction may ensue
- Local lymphadenopathy is common, but spread generally does not occur

**Treatment**

- Options, risks, complications
  - Infections caused by Eumycetes require both surgery and drugs (ketoconazole or itraconazole)
    - Poor response to medical treatment or drugs alone is very common
    - Early surgery with antifungals before and after is often necessary
    - Less data is available for newer antifungals, voriconazole and posaconazole
  - Actinomycotic infections respond better to medical management alone
    - Multiple combinations can be used, but streptomycin alternating with dapsone is most common starting regimen

**Prognosis**

- Small, localized lesions respond well to surgical excision and antifungal therapy
- Advanced lesions with bone involvement often require amputation, and typical drug therapy is often ineffective
- Recurrence rate of eumycetomas varies from 20-90%
- Actinomycetoma cure rate varies from 60-90%

**IMAGING****Radiographic Findings**

- Early lesions show soft tissue granuloma
- Older lesions with bone involvement show bone scalloping, periosteal reaction, and eventually multiple cavities

**MR Findings**

- Dot-in-circle sign is likely to be highly specific (too few case reports currently)
- In hyperintense lesions, presence of central low signal intensity dot
  - Gives rise to dot-in-circle sign
    - Very few case reports but appears to be highly suggestive, unique, and easily recognizable

**MICROSCOPIC****Histologic Features**

- 3 histologic reactions
- Type 1 reaction: Grains surrounded by layer of neutrophils, then layer of chronic inflammatory cells, and finally layer of fibrous tissue
  - Capillaries and venules often have surrounding layers of fibrin

- Type 2 reaction: Very similar to type 1 reaction except innermost neutrophil layer is replaced by giant cells and macrophages engulfing grains
- Type 3 reaction: Well-formed epithelioid granulomas, including Langhans giant cells, occasionally with central remnants of fungi
- Common to see Splendore-Hoeppli phenomenon, which is amorphous, eosinophilic, radially arranged material surrounding mass of hyphae or filamentous bacteria
- Black grains are usually golden brown on H&E staining

### Cytologic Features

- Actinomycete granules are ~ 100 µm in diameter with fine branched filaments ~ 1 µm in diameter
- Eumycetes are filaments wider than 1 µm, often forming mass of hyphae in intercellular cement

### Biopsy Site

- Selection of biopsy site very important: Should center on fistula opening in epidermis

## ANCILLARY TESTS

### PCR

- Available

### Histochemistry

- PAS and GMS are best stains to visualize grains of both Eumycetes and actinomycetes

### Culture

- On Sabouraud, blood and malt extract agar can be done
  - High contamination rate and can be time consuming

## DIFFERENTIAL DIAGNOSIS

### Histological

- Botryomycosis (bacterial pseudomycosis)
  - Most difficult differential
  - Gram stain easily differentiates
    - Grains of eumycetoma do not stain with Gram stain
- Sporotrichosis
  - Often massive pseudoepitheliomatous hyperplasia (PEH)
  - Dermal granulomatous inflammation
  - Fungal organisms not always demonstrable, even with special stains
  - Culture or proper clinical history and lymphocutaneous spread diagnostic
- Chromomycosis
  - Often PEH
  - Granulomatous chronic inflammation
  - Characteristic medlar/muriform bodies that resemble copper pennies
  - Culture is confirmatory
- Subcutaneous phaeohyphomycosis
  - Secondary to trauma and inoculation of fungal elements from soil, wood splinters, or thorns
  - Brown pigmented (dematiaceous), branching septate hyphae on histology
  - Culture necessary to definitively identify causative organism

- However, phaeohyphomycetes are common airborne contaminants so supportive histology &/or clinical history helpful

- Hyalohyphomycosis

- Hyaline, nondematiaceous, branched, septate mycelial fungal organisms with similar morphology to *Aspergillus* species
  - Hyphal elements difficult to distinguish on H&E
  - Special stains such as PAS or GMS are necessary
- Culture necessary to identify causative agent
  - However, hyalohyphomycetes are common airborne contaminants so supportive histology &/or clinical history helpful

- Majocchi granuloma

- Rare type of deep folliculitis due to dermatophytes
- Typically on lower legs (especially young females who shave frequently)
- Deep suppurative and granulomatous folliculitis
  - *Trichophyton* species demonstrable with special stains (PAS, GMS)

### Clinical

- Osteomyelitis
  - More common than mycetoma in temperate climates
  - Bacterial culture positive
  - Bone scan shows bone involvement
- Deep fungal infection
  - Positive culture and special stains on histopathology for fungus
  - When primary in skin then history of trauma
- Squamous cell cancer
  - Sun-exposed skin
  - Fair-skinned patient with history of marked chronic sun exposure
  - Would mimic mycetoma especially in neglected, chronic tumor
- Actinomycosis
  - Often on face and neck (lumpy jaw)
    - Can also be seen on chest, abdominal wall, and genital area
  - Positive culture and histopathology for actinomycosis
- Tuberculosis
  - Positive culture and sometimes special stains for tuberculin bacilli
  - Not more common in tropical and subtropical region
  - Not more common on feet

## SELECTED REFERENCES

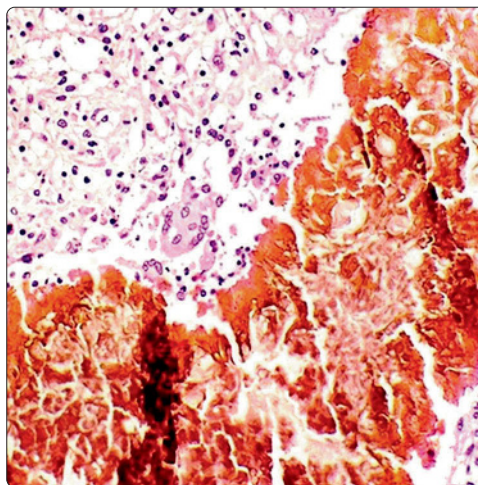
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**Multiple Draining Sinus Tracts With Hyperpigmentation**



**Black Grains Indicative of Eumycetoma**

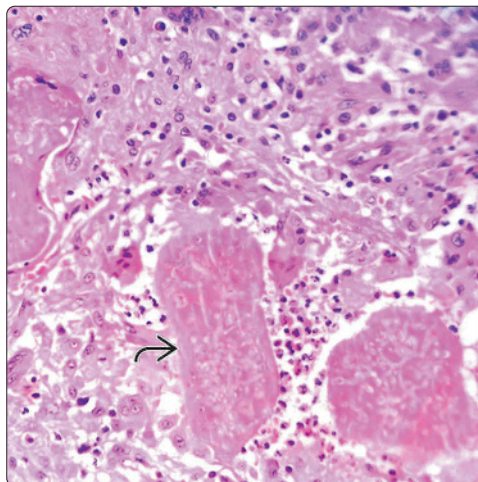


(Left) This patient with mycetoma presented with a hyperpigmented, edematous, boggy, medial ankle with multiple sinus tracts [arrow] indicative of Madura foot. (Right) Eumycetomas can have either black or pale grains. Pale grains can also be seen in actinomycetomas, but black grains (which stain brown on H&E) are characteristic of eumycetomas.

**Black Grains With Filamentous Fungi**

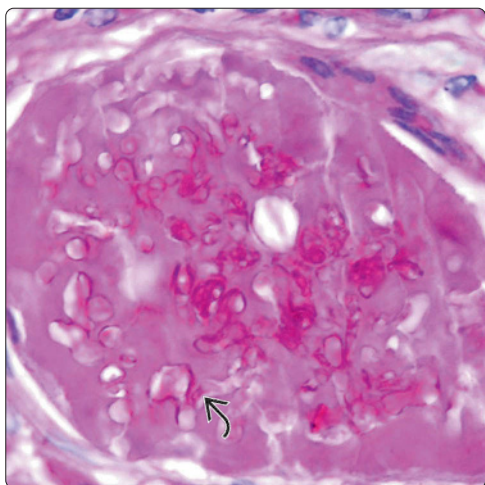


**Light Pink Pale Grains on H&E**

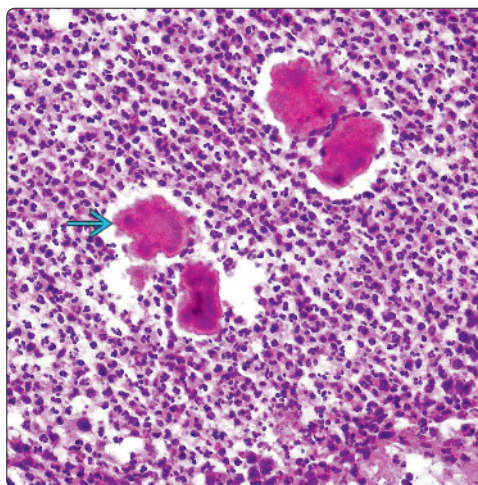


(Left) This image shows characteristic black grains (brown on H&E) of eumycetoma surrounded by acute inflammation. Note how the filamentous fungi [arrow] form a thick mass. (Courtesy C. Rosales, MD.) (Right) Higher power view shows another case of eumycetoma with pale grains [arrow] that usually stain light pink or light purple on H&E, with neutrophils and chronic inflammatory cells.

**Dense Mass of Intermeshing Hyphae Creates Pale Grains**



**Mycetoma Due to Actinomycetes [Gram(+) Bacteria]**



(Left) High-power view of a pale grain of eumycetoma demonstrates a dense mass of intermeshing hyphae [arrow] in intercellular cement. (Right) Mycetoma can also be due to actinomycetes (actinomycetomas) [arrow]. The small filamentous bacteria (usually  $\leq 1 \mu\text{m}$ ) will stain positively on Gram. Culture also helps differentiate from cases of eumycetoma. (Courtesy M. Chaffins, MD.)



# Paracoccidioidomycosis

## KEY FACTS

### TERMINOLOGY

- Systemic mycosis, autochthonous to Latin America

### CLINICAL ISSUES

- 2 clinical presentations
  - Juvenile acute form with reticuloendothelial involvement from zero to multiple skin lesions
  - Adult chronic form with pulmonary and extrapulmonary manifestations
- Cutaneous lesions ranging from papular umbilicated lesions to warty lesions to exudative &/or vegetative-ulcerative nodules

### MICROSCOPIC

- Pseudoepitheliomatous hyperplasia with granulomatous pattern
- Double-membrane wall roundish cells, birefringent, with multiple narrow-necked buds

- Fungus recognized by its roundish yeasts with pilot's/mariner's wheel appearance

### ANCILLARY TESTS

- Immunodiffusion
- Complement fixation test
- Immuno-electrophoresis
- Enzyme-linked immunosorbent assay (ELISA)
- Western blot

### TOP DIFFERENTIAL DIAGNOSES

- Histoplasmosis
- Coccidioidomycosis
- Chromoblastomycosis
- North American blastomycosis
- Lobomycosis
- Protothecosis

Multiple Molluscum-Like Papules on Face

(Left) A patient with juvenile-type paracoccidioidomycosis (PCM) demonstrates multiple molluscum-like papules on the face. (Right) This patient with juvenile PCM demonstrates numerous ulcerated nodules on the neck (flexural areas).

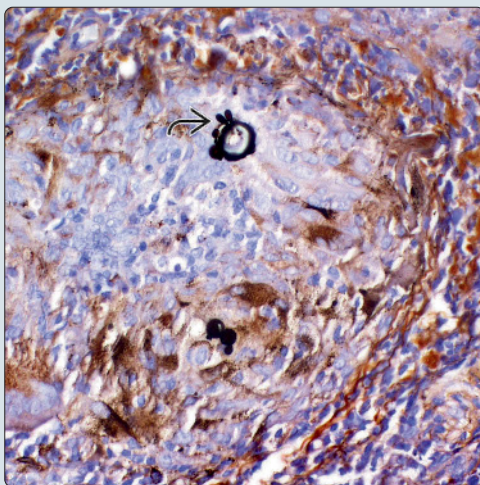


Ulcerated Nodules in Juvenile Paracoccidioidomycosis

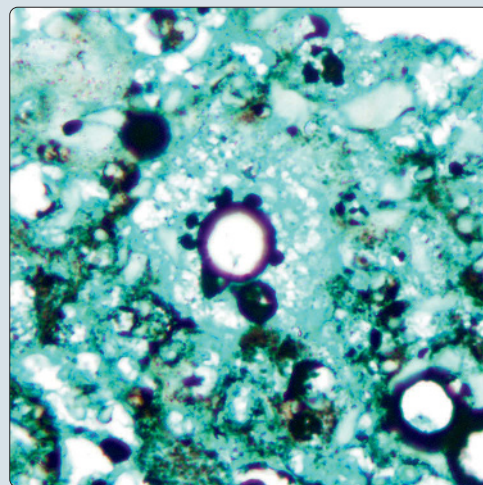


Mariner's Wheel With Narrow Buds Emanating From Large Round Cells

(Left) Although rarely found in biopsy specimens, the double membrane wall with multiple narrow buds emanating from it is often likened to a mariner's or pilot's wheel and is pathognomonic for paracoccidioidomycosis. (Right) GMS stain shows the double-membrane birefringent wall of roundish cells with multiple narrow-necked buds resembling a pilot's/mariner's wheel. (Courtesy E. Montgomery, MD.)



High-Power View of Pilot's Wheel





## TERMINOLOGY

### Abbreviations

- Paracoccidioidomycosis (PCM)

### Synonyms

- South American blastomycosis, Lutz-Splendore de Almeida disease

### Definitions

- Systemic mycosis, autochthonous to Latin America

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- *Paracoccidioides brasiliensis* (dimorphic fungus)

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Highest incidence in South American countries
    - Brazil, Colombia, Venezuela, Paraguay, Peru, and Argentina
- Sex
  - Predominantly affects males in economically productive years (30-60 years of age)

### Presentation

- 2 clinical forms
  - Juvenile type
    - Occurs in younger and immunocompromised patients as subacute disease
    - Accounts for 3-5% of PCM cases
    - Most commonly multiple papular and ulcerated lesions on face and folds
  - Chronic or adult type
    - Most common clinical form (90% of cases)
    - Presents with pulmonary and extrapulmonary involvement
    - Mucous membrane lesions found in 50% of cases
- Skin alterations are polymorphic ranging from papular, molluscum-like, or warty lesions to exudative &/or ulcerative-vegetative nodules
- Cutaneous lesions in PCM reported to occur in 30-54% of patients
  - Originate from preexisting contiguous lesion, from hematogenous dissemination, or rarely by direct penetration of fungus through skin
- Sequelae of PCM
  - Chronic obstructive pulmonary disease (COPD), dysphonia or laryngeal obstruction, reduced mouth opening, adrenal gland dysfunction

### Natural History

- Acquired through inhalation, fungus can spread to other organs through lymphohematogenous dissemination
- In immunocompetent patients, fungus remains in latent state, and after prolonged period infection might progress to chronic form in adults
- Less commonly, disease might progress from primary focus and develop into acute or subacute form in children or adolescents

## Treatment

- Drugs
  - Itraconazole, sulfamethoxazole-trimethoprim, ketoconazole, amphotericin B
  - Long-term treatment is required

## Prognosis

- Juvenile form carries poor prognosis, and adult form is chronic with better prognosis

## MICROSCOPIC

### Histologic Features

- Chronic granulomatous dermatitis with pseudoepitheliomatous epidermal hyperplasia (PEH) and intraepidermal abscesses

### Cytologic Features

- Double-membrane wall, roundish cells, birefringent, with multiple narrow-necked buds
  - Appearance has been described as resembling pilot's/mariner's wheel

## ANCILLARY TESTS

### Serologic Testing

- Immunodiffusion, complement fixation test, immunoelectrophoresis, enzyme-linked immunosorbent assay (ELISA), and Western blot are available

## DIFFERENTIAL DIAGNOSIS

### Histoplasmosis

- Numerous macrophages containing 2- to 4-µm rounded to oval organisms surrounded by clear space within cytoplasm

### Coccidioidomycosis

- Multiple spherules varying in size from 5-80 µm with numerous endospores within larger spherules

### Chromoblastomycosis

- Characteristic medlar bodies singly or in pairs of tetrads resembling copper pennies

### North American Blastomycosis

- Similar PEH with microabscesses but with thick-walled spores demonstrating broad-based budding
- Different geographic distribution

### Lobomycosis

- Characteristic long chains of rounded and hyaline cells joined by small tubule and thick birefringent walls

### Protothecosis

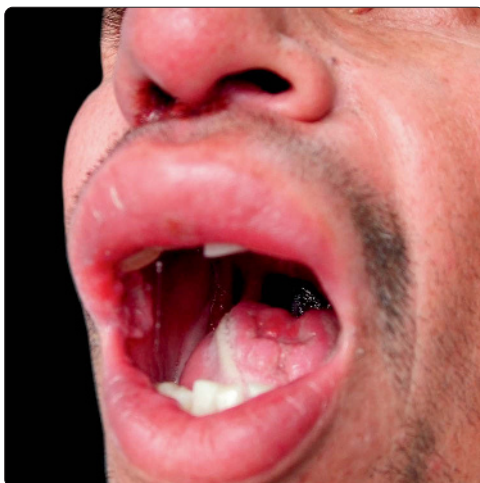
- Thick-walled spherical bodies 3-11 µm, often with clear halo and occasionally cartwheel appearance with morula-like septations

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1. de Souza SP et al: Paracoccidioidomycosis in southern Rio Grande do Sul: a retrospective study of histopathologically diagnosed cases. *Braz J Microbiol.* 45(1):243-7, 2014
2. López-Martínez R et al: Paracoccidioidomycosis in Mexico: clinical and epidemiological data from 93 new cases (1972-2012). *Mycoses.* 57(9):525-30, 2014

## Ulcerative Lesions of Adult-Type Paracoccidioidomycosis

(Left) Classical facies of a patient with adult-type chronic PCM shows predominantly oral involvement compared to the nasal involvement seen in leishmaniasis. Note the painful ulcerations on buccal mucosa and tongue. (Right) Warty lesions are shown on the sole of this patient with juvenile-type PCM.

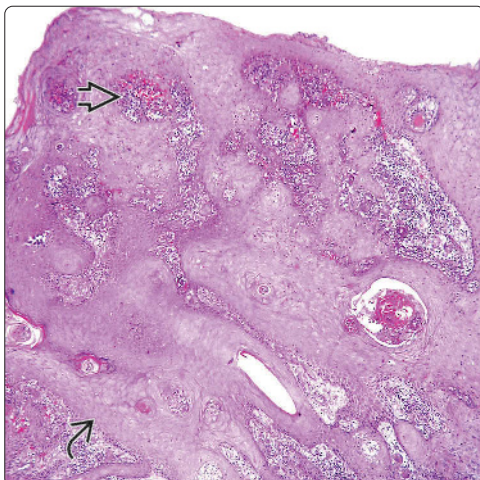


## Warty Lesions on Sole of Foot

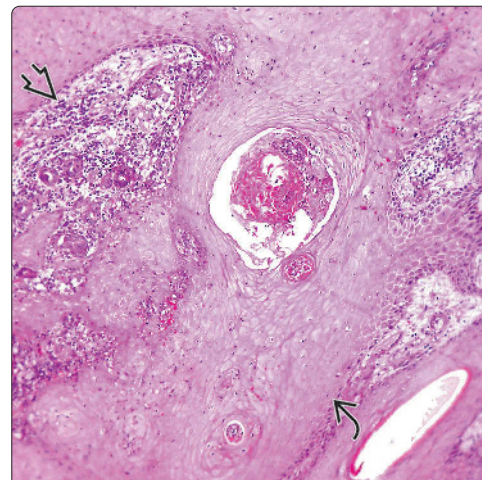


## Pseudoepitheliomatous Hyperplasia With Microabscesses

(Left) On lower power, paracoccidioidomycosis demonstrates significant pseudoepitheliomatous hyperplasia and intraepidermal abscesses typical of deep fungal infection. (Right) A slightly higher power view shows pseudoepitheliomatous hyperplasia and neutrophilic intraepidermal abscesses, which are a good place to look for the fungi.

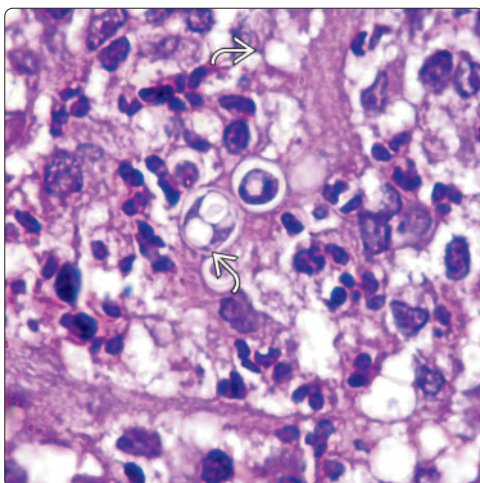


## Pseudoepitheliomatous Hyperplasia and Intraepidermal Abscesses

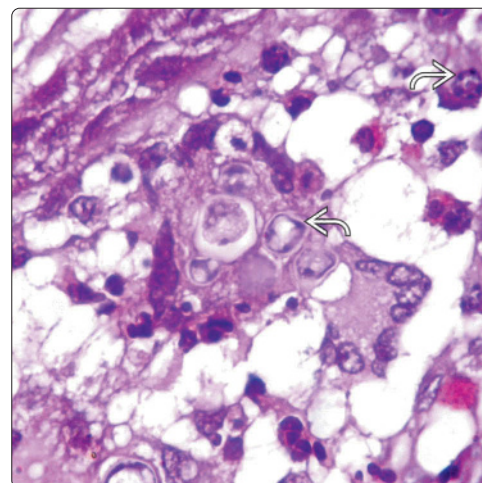


## Large Yeasts With Satellite Buds

(Left) High-power view of paracoccidioidomycosis demonstrates multiple satellite buds emerging from a central yeast. Although more difficult to appreciate on H&E, note the thin budding necks. (Right) High-power view of paracoccidioidomycosis shows roundish yeast with the classical pilot's/mariner's wheel appearance in a multinucleated giant cell.

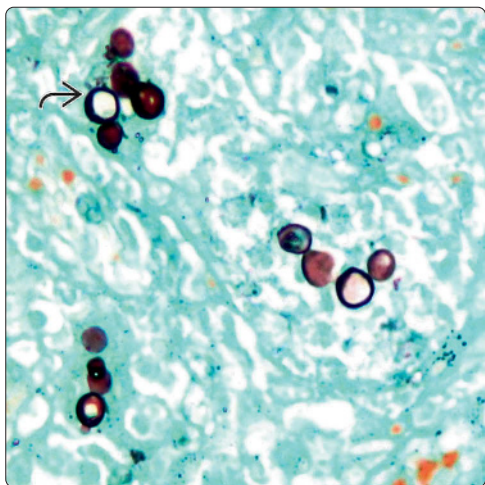


## Large Roundish Yeasts Within Giant Cells

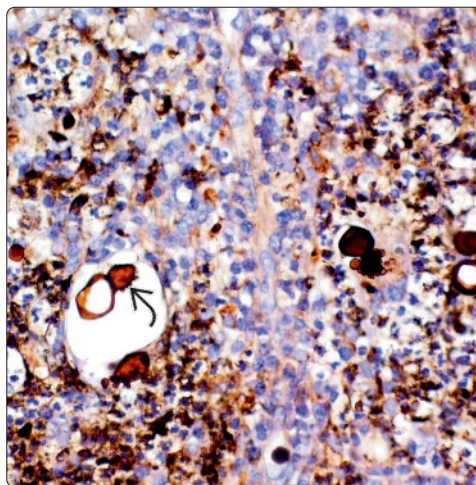






**Roundish Yeasts With Narrow Budding Necks**

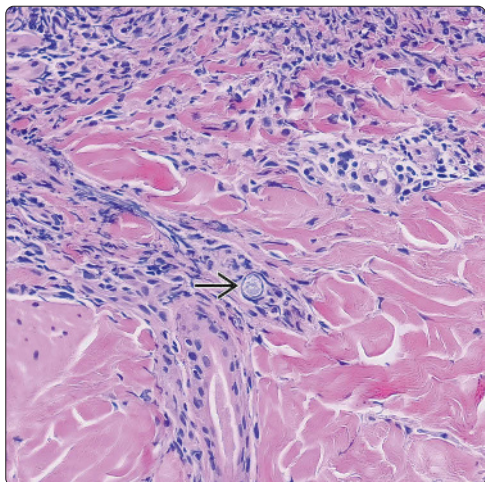


**Narrow Budding Necks, GMS Stain**

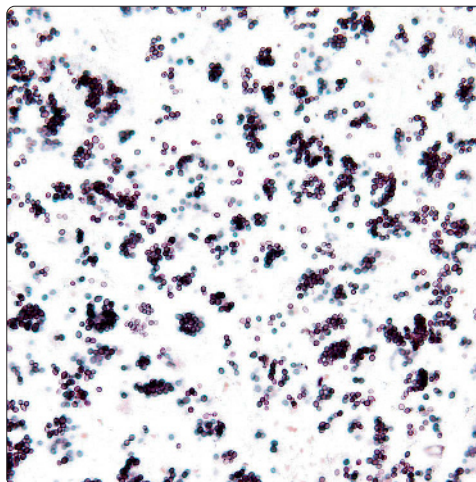



(Left) GMS stain much more easily elucidates the multiple budding yeasts with thin budding necks , characteristic of *P. brasiliensis*. (Right) Another case of paracoccidioidomycosis on GMS stain demonstrates numerous narrow budding necks . (Courtesy S. Billings, MD.)

**Larger Spherules of Coccidioidomycosis With Endospores**

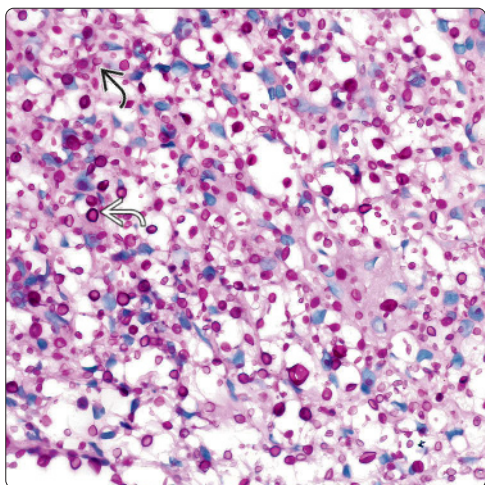


**Narrow-Based Budding Yeasts of Histoplasmosis, GMS Stain**

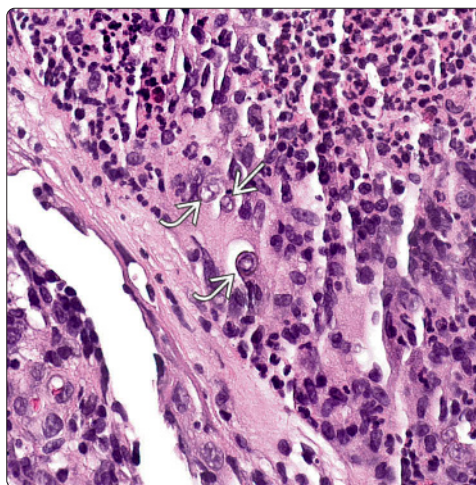






(Left) *Coccidioidomycosis* spherules  can be much larger than paracoccidioidomycosis (up to 80  $\mu$ m in size) with endospores in larger spherules. Smaller spherules such as this one, however, can be a histologic mimic. (Courtesy P. LeBoit, MD.) (Right) GMS stain from a case of cutaneous histoplasmosis demonstrates similar roundish yeast that display narrow-based budding. However, histo does not demonstrate multiple narrow neck buds. Culture may be necessary to differentiate. (Courtesy L. Thompson, MD.)

**Mucicarmine Positive Capsule of Cryptococcus**



**Thick-Walled Spores of Blastomycosis**



(Left) *Cryptococcus* can sometimes be confused with coccidioidomycosis, but crypto is unusual in the fungal world in that it shows a characteristic mucicarmine positive capsule . It also reproduces via narrow neck budding . (Right) Blastomycosis demonstrates thick-walled fungal spores  with characteristic broad-based budding  also amidst neutrophilic microabscesses; however, the distribution of the organisms is often further north in the Mississippi and Ohio River valleys.



## KEY FACTS

## ETIOLOGY/PATHOGENESIS

- Causative agent: Fungus *Lacazia loboi*
- Habitat somewhere in rural environment
- Introduced directly into dermis through injury

## CLINICAL ISSUES

- Disease of insidious character
- Typical lesions are keloidiform nodules in ear, "keloids over keloids"

## MICROSCOPIC

- Epidermis is usually atrophic
  - Pseudoepitheliomatous hyperplasia is common in vegetating lesions
- Dermis shows diffuse nonnecrotic granulomatous lesions composed of foreign bodies, macrophages, and multinucleated giant cells containing typical thick-walled yeast



- Plasmacytic and neutrophilic infiltrate seen in ulcerated lesions
- *Lacazia loboi* forms long chains of rounded and hyaline cells, each joined by small tubule with thick and birefringent cell wall

## ANCILLARY TESTS

- Diagnosis made by direct examination of fungus in tissue smear from lesion or by histopathology

## TOP DIFFERENTIAL DIAGNOSES

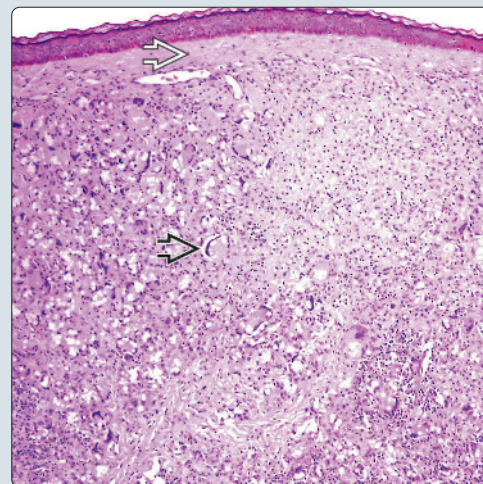
- Deep fungal infections
  - Paracoccidioidomycosis
    - Fungal organisms may appear similar
    - Lesions typically affect central face and mucous membranes
  - Identification of characteristic thick-walled yeast of *L. loboi* in patient from endemic area necessary to differentiate from similar clinical and histopathologic entities




(Left) *Lobomycosis* clinically shows confluent keloidal lesions on the anterior region of the outer ear, which is a frequent location. (Right) *Lobomycosis* shows an atrophic epidermis with a grenz zone . The dermis shows fibrosis and a diffuse infiltrate of macrophages and multinucleated giant cells .

Confluent Keloidal Lesions on Outer Ear

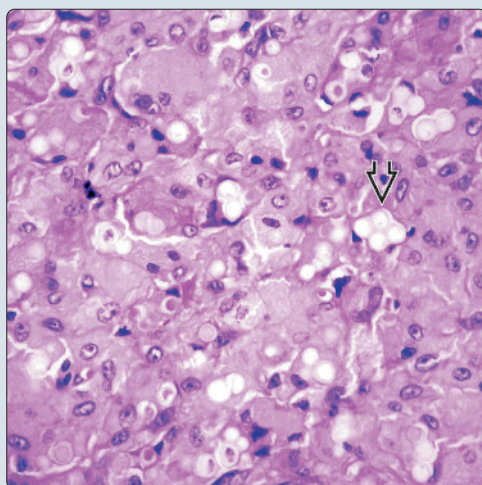


Diffuse Dermal Infiltrate of Histiocytes and Giant Cells

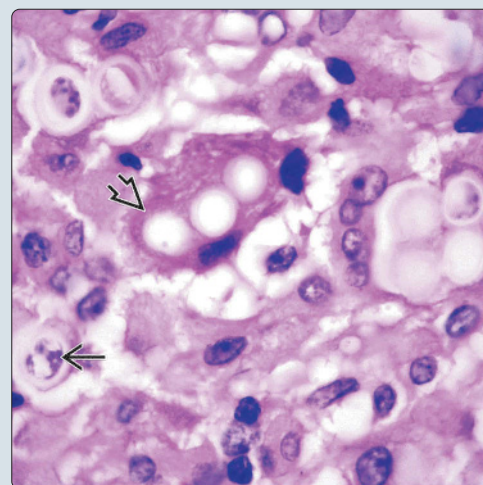


(Left) Chains of yeast cells can be seen surrounded by clear halos, forming pairs, trios, and even in groups of 4 , inside multinucleated giant cells. (Right) The fungi have a thick wall  and form a single chain with individual cells joined by a narrow, tubule-like projection. The staining of the cytoplasmic contents  is an indication of viable cells.

Chains, Trios, and Tetrads of Yeast



Chains and Tetrads of Yeast With Thick Walls





## TERMINOLOGY

### Synonyms

- Keloidal blastomycosis, Jorge Lobo disease, lacaziosis

### Definitions

- Chronic, granulomatous fungal disease caused by *Lacazia loboi* that affects skin and subcutaneous tissue

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- *Lacazia loboi* is intracellular agent known to cause disease in humans, salt water and fresh water dolphins
- Soil and vegetation are likely sources of infection
- *L. loboi* accesses skin by penetration or accidental trauma such as thorn prick or insect bite
- Once in dermis, fungus is phagocytized, initiating slow-growing process of multiplication
- Some suggest lymphatic dissemination, although hematogenous and contiguity are also hypotheses

## CLINICAL ISSUES

### Epidemiology

- Age
  - Wide range (12-70 years); reports in children 1 year old
- Sex
  - Clear preponderance of males (90% of cases presented in literature)
- Ethnicity
  - No ethnic predominance has been described
  - Disease is endemic in Brazilian Amazon and tropical countries in South and Central America
  - People who carry out agricultural activities, as well those dedicated to fishing, hunting, and mining, are at risk for infection

### Site

- Lesions predominantly appear on exposed areas
- Most affected area is pinna of ear followed by lower limbs and upper limbs

### Presentation

- Keloidal nodular form is most frequent
  - Verrucous lesions are also common
- Ulcerations, gummatous and sclerodermiform lesions are not common
- Lesions may be single or multiple, localized or disseminated
  - Regional lymph nodes may also be involved
- Mucous membranes and internal organs are typically not involved

### Laboratory Tests

- Diagnosis is made by identification of fungus on direct examination or biopsy
- Direct examination reveals abundance of round yeast fungi with thick, refractile, double contour walls
  - Rosary or chain pattern is frequent

### Treatment

- Surgical approaches

- Treatment of choice for isolated lesions is surgery with wide margins
  - Cryosurgery is another option
- Drugs
  - Clofazimine 300 mg/d at beginning and 100 mg/d for at least 2 years after clinical improvement
  - Clofazimine at 100 mg/d in association with itraconazole 100 mg/d for 1 year has also been used with good results

### Prognosis

- Slowly progressive chronic fungal infection

## MICROSCOPIC

### Histologic Features

- Epidermis is usually atrophic
  - Pseudoepitheliomatous hyperplasia is common in vegetating lesions
- Dermis shows diffuse nonnecrotic granulomatous lesions composed of foreign bodies, macrophages, and multinucleated giant cells containing typical, thick-walled yeast
- Plasmacytic and neutrophilic infiltrate seen in ulcerated lesions

### Cytologic Features

- *Lacazia loboi* forms long chains of rounded and hyaline cells, each joined by small tubule with thick and birefringent cell wall

## ANCILLARY TESTS

### Serologic Testing

- High sensitivity but lacks specificity because of antigenic cross reactivity with *Paracoccidioides*

### Special Stains

- PAS, GMS, and Grocott-Gomori stains clearly distinguish yeast-like cells in skin tissues

### Culture

- Not useful; cannot be isolated

## DIFFERENTIAL DIAGNOSIS

### Multiple Entities

- Deep fungal infections
  - Paracoccidioidomycosis
    - Fungal organisms may appear similar histopathologically
    - Lesions typically affect central face and mucous membranes

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Granulomatous pattern with chains of rounded and hyaline cells with double and birefringent membrane

## SELECTED REFERENCES

1. Arju R et al: Jorge Lobo's disease: a case of keloidal blastomycosis (lobomycosis) in a nonendemic area. *Ther Adv Infect Dis*. 2(3-4):91-6, 2014
2. Papadavid E et al: Lobomycosis: A case from Southeastern Europe and review of the literature. *J Dermatol Case Rep*. 6(3):65-9, 2012

## KEY FACTS

### TERMINOLOGY

- Tropical mucocutaneous infection caused by water mold *Rhinosporidium seeberi*

### ETIOLOGY/PATHOGENESIS

- *R. seeberi* is not fungus but protist belonging to group Mesomycetozoea

### CLINICAL ISSUES

- Most commonly presents as painless nasal polyps
- Skin, conjunctiva, larynx, oral mucosa, and genitalia are less common sites

### MICROSCOPIC

- Dermal acute and chronic granulomatous inflammation and often granulation tissue are seen surrounding sporangia
- Intact and ruptured, huge spherical sporangia measuring (50-300  $\mu$ m) with numerous endospores and thick, PAS-positive chitinous walls are characteristic

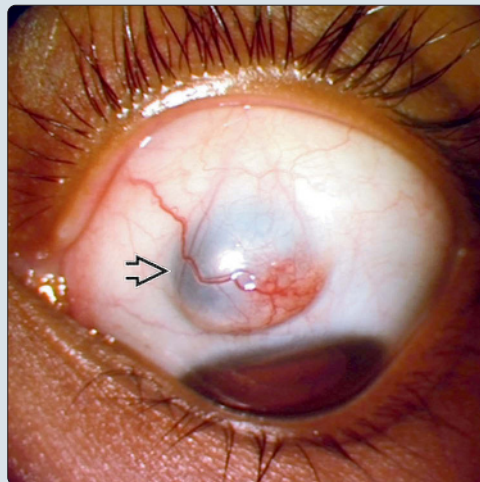
- Endospores are spherical to oval, measure 6-12  $\mu$ m, stain purple on H&E, and can be seen within sporangia or free within tissue
- Sporangia begin as immature forms (10-100  $\mu$ m), grow to larger mature forms (100-300  $\mu$ m), and eventually rupture
- Rupture releases endospores, eliciting foreign body and neutrophilic reaction in tissue

### TOP DIFFERENTIAL DIAGNOSES

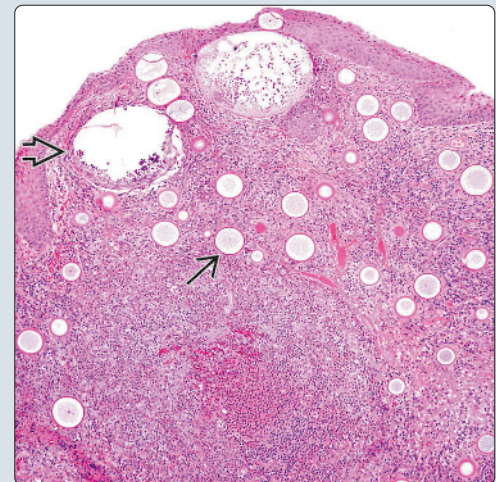
- Coccidioidomycosis
  - Sporangia are much smaller (5-80  $\mu$ m vs. 50-300  $\mu$ m for rhinosporidiosis)
  - Endospores usually not present vs. usually present in rhinosporidiosis
- Myospherulosis
  - Sac-like structures (spherules) with lipid membrane containing altered red blood cells that do not stain with GMS or PAS (vs. *R. seeberi*)

**Scleral Staphyloma From Infection With Rhinosporidiosis**

(Left) This image shows a scleral staphyloma (bulging of the sclera) due to inflammation from infection with *Rhinosporidium seeberi*. (Courtesy J. Biswas, MD.) (Right) Mucosal rhinosporidiosis demonstrates huge mature sporangia with associated endospores. Smaller, more immature sporangia are also seen. (Courtesy G. Ellis, DDS.)

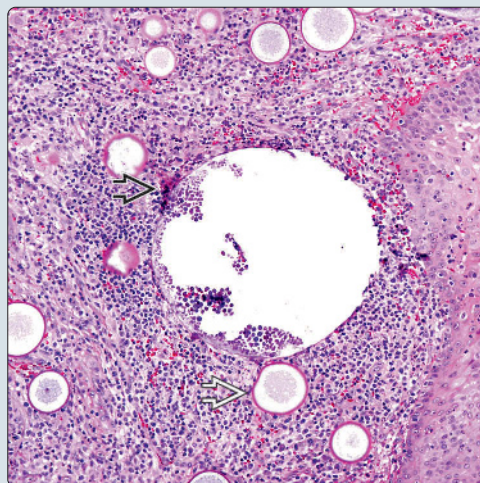


**Huge Mature Sporangia With Endospores**

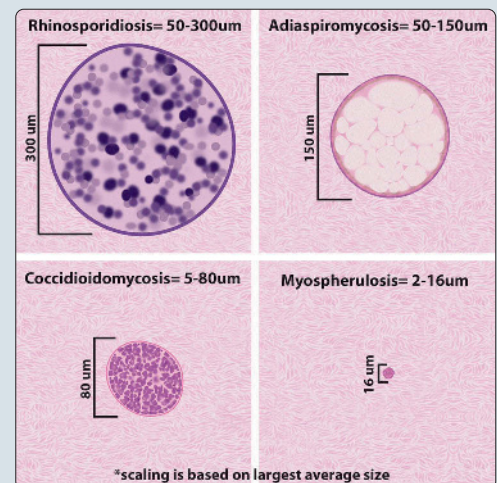


**Immature and Mature Sporangia With Endospore Release**

(Left) High-power view shows a large mature sporangia releasing endospores amidst acute and chronic granulomatous inflammation. Smaller, more immature forms with thick chitinous walls that would stain PAS positive are also seen. (Courtesy G. Ellis, DDS.) (Right) All 4 major histologic differential diagnoses are listed in this image. Although much larger than its mimics, mature sporangia of rhinosporidiosis are not always seen in tissue.



**Size Comparison of Most Common Histopathologic Mimics**





**TERMINOLOGY****Definitions**

- Tropical mucocutaneous infection caused by water mold *Rhinosporidium seeberi*

**ETIOLOGY/PATHOGENESIS****Infectious Agents**

- *R. seeberi* is not fungus but protist belonging to group Mesomycetozoea
  - Aquatic and may be transmitted via fresh water, usually in tropical area (southern India, Sri Lanka, northeastern Brazil)
- Transmission is not yet known
  - Spores hypothesized to spread through air and water to humans from animal sources
    - Bathing in stagnant water where domestic animals are washed is risk factor

**CLINICAL ISSUES****Epidemiology**

- Sex
  - Overall involvement and nasal involvement more common in men
  - Ocular involvement more common in women
- Ethnicity
  - Disease is endemic in India, Sri Lanka, South America, and Africa
  - Cases also described in USA and Iran

**Presentation**

- Most commonly presents as painless nasal polyps that become hyperplastic and studded with flecks of red and white dots
- Conjunctiva, larynx, oral mucosa, skin, and genitalia are less commonly involved sites
- Cutaneous lesions can be papillomatous, sessile, or pedunculated with ulceration
  - Ulcerated lesions can mimic squamous cell carcinoma and basal cell carcinoma
  - Warty lesions mimic verrucae
- Cutaneous lesions may take 1 of 3 forms
  - Primary cutaneous (quite rare)
    - Can be solitary or multiple on face, extremities, scalp, or rarely other sites
  - Satellite lesions surrounding nasal mucosal involvement
  - Disseminated lesions ± nasal lesions

**Treatment**

- Excision with cauterization of base

**Prognosis**

- 20% recur after surgical excision and intralesional amphotericin B has been used to prevent rare visceral dissemination
  - Repeated excisions may be required over years

**MICROSCOPIC****Histologic Features**

- Pedunculated lesion with papillomatous hyperplastic epithelium
- Dermal acute and chronic granulomatous inflammation and often granulation tissue are seen surrounding sporangia
- Intact and ruptured, huge spherical sporangia measuring (50-300 µm) with numerous endospores and thick, PAS-positive chitinous walls are characteristic
  - Endospores are spherical to oval, measure 6-12 µm, stain purple on H&E, and can be seen within sporangia or free within tissue
  - Sporangia begin as immature forms (10-100 µm), grow to larger mature forms (100-300 µm), and eventually rupture
  - Rupture releases endospores, eliciting foreign body and neutrophilic reaction in tissue

**Cytologic Features**

- Within endospores, numerous eosinophilic globular bodies can often be seen

**ANCILLARY TESTS****Histochemistry**

- GMS, PAS, and mucicarmine all help stain organisms

**DIFFERENTIAL DIAGNOSIS****Histopathologic**

- Coccidioidomycosis
  - Sporangia are much smaller (5-80 µm vs. 50-300 µm for rhinosporidiosis)
    - Endospores usually not present vs. usually present in rhinosporidiosis
  - No globular bodies
- Myospherulosis
  - Sac-like structures (spherules) with lipid membrane containing altered red blood cells that do not stain with GMS or PAS (vs. *R. seeberi*)
  - Endospores of rhinosporidiosis are 2x size of erythrocytes
  - Spherules may be more elliptical or irregular and range in size from 2-16 µm (vs. 50-300 µm for rhinosporidiosis)
- Adiaspiromycosis
  - Exceedingly rare fungal infection in lung and mucosal sites due to *Chrysosporium* spp.
  - Histology shows large, thick-walled, PAS(+) adiaspores ranging from 50-150 µm in size
  - No purely cutaneous cases to date

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1. Chatterjee K et al: A curious ulcer on the pinna: rhinosporidiosis at an unusual place. *Int J Dermatol*. 54(7):e277-9, 2015
2. Ashique KT et al: Strawberry-shaped lesion on the chest: cutaneous rhinosporidiosis. *Indian Dermatol Online J*. 5(Suppl 2):S125-7, 2014
3. Fernandez-Flores A et al: Morphological findings of deep cutaneous fungal infections. *Am J Dermatopathol*. 36(7):531-53; quiz 554-6, 2014
4. Vallarelli AF et al: Rhinosporidiosis: cutaneous manifestation. *An Bras Dermatol*. 86(4):795-796, 2011

## KEY FACTS

### TERMINOLOGY

- General term for infections caused by dematiaceous (pigmented) filamentous fungi containing melanin in their cell walls

### ETIOLOGY/PATHOGENESIS

- Causative agents are dematiaceous (pigmented) fungi found ubiquitously in soil

### CLINICAL ISSUES

- Wide variety of presenting symptoms and diseases

### MICROSCOPIC

- Brown pigmented hyphae within dermis with associated mixed inflammation is diagnostic
- Granulomatous inflammation is common
- GMS and PAS special stains can highlight fungal elements, but will obscure pigment
- Fontana-Masson special stain can highlight melanin pigment within fungal elements

### ANCILLARY TESTS

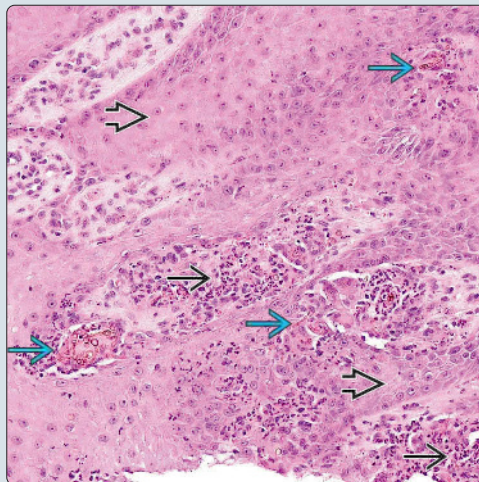
- Fungal culture with speciation required for definitive diagnosis

### TOP DIFFERENTIAL DIAGNOSES

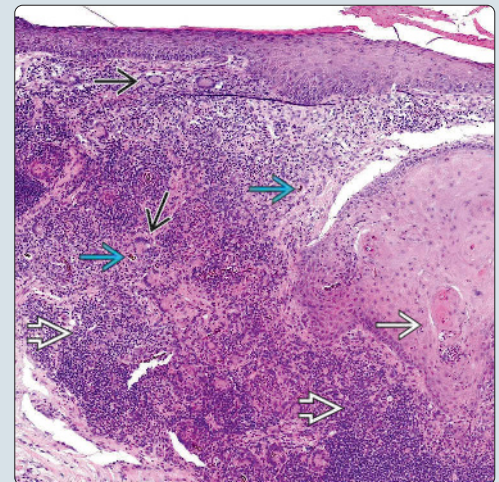
- Chromoblastomycosis
  - Pathognomonic finding is pigmented sclerotic bodies (a.k.a. septate bodies, medlar bodies, muriform cells)
- Eumycetoma
  - Chronic granulomatous inflammation and sinus tract formation with drainage to skin surface
- Botryomycosis (bacterial pseudomycetoma)
  - Chronic bacterial infection

**Pseudoepitheliomatous Hyperplasia With Pigmented Fungi**

(Left) Pseudoepitheliomatous hyperplasia with acute inflammatory cell infiltrate associated with collections of pigmented fungal elements is a classic histologic appearance of phaeohyphomycotic infections. (Right) Dense mixed inflammation with giant cell reaction associated with darkly pigmented fungal hyphae and associated pseudoepitheliomatous hyperplasia is shown.



**Giant Cell Reaction With Pigmented Fungal Hyphae**

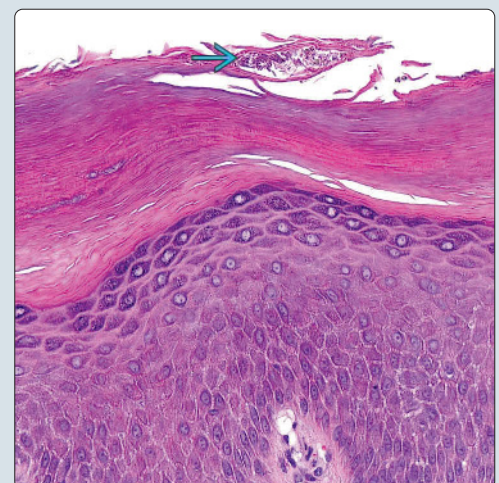


**Pigmented Hyphae Within Multinucleated Giant Cell**

(Left) Higher magnification shows pigmented fungal elements within a multinucleated giant cell. (Right) Pigmented fungal elements in the stratum corneum, indicative of tinea nigra, are shown.



**Pigmented Hyphae of Tinea Nigra**





## TERMINOLOGY

### Definitions

- Term phaeohyphomycosis was introduced by Ajello et al in 1974
- General term for infections caused by dematiaceous (pigmented) filamentous fungi containing melanin in their cell walls

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- Often associated with trauma involving exposure to soil &/or plants (car accidents, tornado survivors)
- Agents of phaeohyphomycosis are found worldwide and are predominantly soil organisms

### Infectious Agents

- Attributed to > 100 species and 60 genera of fungi
  - Most are opportunistic pathogens
  - Most common cause is *Scedosporium prolificans*

## CLINICAL ISSUES

### Epidemiology

- Impaired host immunity is still considered risk factor
- Over 50% of cases occur in immunocompetent patients

### Site

- Causes variety of clinical manifestations depending on site and extent of involvement

### Presentation

- Superficial infection
  - Most common form of infection
  - Associated with minor trauma or other environmental exposure
- Onychomycosis
  - Involvement of 1-2 nails with lack of response to traditional therapy
- Subcutaneous lesions
  - Occur on exposed areas of skin as solitary abscess or granuloma at sites of penetrating trauma
  - May involve joints or bones

### Treatment

- Drugs
  - Amphotericin B is considered empiric and definitive therapy
  - 2nd-line agents include itraconazole, terbinafine, voriconazole, posaconazole, and ravuconazole
  - For CNS involvement, combination therapy with amphotericin B, flucytosine, and itraconazole and surgery is required
  - Duration of therapy based on clinical response; can range from weeks to months or longer

### Prognosis

- Overall mortality is 79%
  - Mortality rate is 84% in immunocompromised patients
  - Mortality rate is 65% in immunocompetent patients

## MACROSCOPIC

### General Features

- Varies depending on site of infection

## MICROSCOPIC

### Histologic Features

- Brown pigmented hyphae within dermis with associated mixed inflammation is diagnostic
- Granulomatous inflammation is common
- GMS and PAS special stains can highlight fungal elements but will obscure pigment
- Fontana-Masson special stain can highlight melanin pigment within fungal elements

## DIFFERENTIAL DIAGNOSIS

### Chromoblastomycosis

- Chronic, slowly progressing skin and subcutaneous fungal infection
- Associated with traumatic inoculation by vegetation (thorns or splinters)
- Pathognomonic finding is pigmented sclerotic bodies (a.k.a. septate bodies, medlar bodies, muriform cells)
  - Light brown, thick-walled, round cells, clumped or stacked together, so-called copper pennies
  - 4-12  $\mu$ m (size of 1-2 RBCs)
  - Associated with mixed inflammation with neutrophils

### Eumycetoma

- Chronic granulomatous fungal infection, predominately of extremities
  - Madura foot: Fungal mycetoma of foot
- Traumatic inoculation of fungal spores
- Chronic granulomatous inflammation and sinus tract formation with drainage to skin surface

### Botryomycosis (Bacterial Pseudomycetoma)

- Chronic bacterial infection
- *Staphylococcus aureus* is most common associated bacteria

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Culture and microscopic examination are definitive methods to identify fungi
  - Melanin-specific stains, such as Masson-Fontana, can be used to confirm presence of dematiaceous hyphae in tissue

### Laboratory Studies

- Definitive speciation can be difficult because causative agents are often considered contaminants when isolated from culture

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# Penicilliosis

## KEY FACTS

### TERMINOLOGY

- *Penicillium marneffei* infection

### ETIOLOGY/PATHOGENESIS

- Endemic in Southeast Asia
- Thermally dimorphic fungus

### CLINICAL ISSUES

- Majority of skin lesions are papules with central necrotic umbilication
- Nonspecific reticuloendothelial cell infection (should highly suspect with travel history)
  - Dyspnea, cough, fever
  - Generalized lymphadenopathy, hepatosplenomegaly
  - Diarrhea
- With dissemination, skin, joints, and bone may become infected
  - Papules on face, chest, arms, and legs may occur in ~ 70% of disseminated patients

- Appear similar to lesions of molluscum contagiosum

### MICROSCOPIC

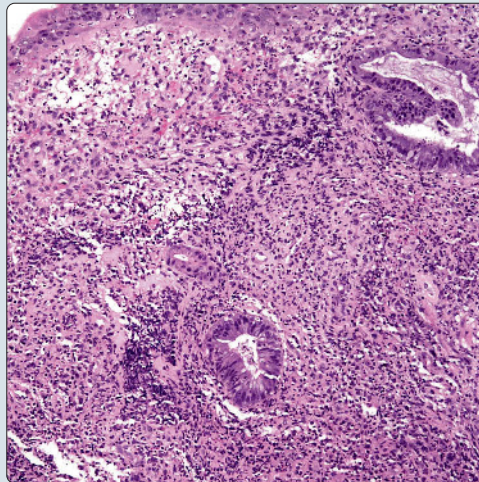
- ~ 5- $\mu$ m capsular-shaped yeast-like arthroconidia with central septa
  - Routine H&E stain may produce false capsule (confusing with *Histoplasma*)
  - Silver stains and periodic acid-Schiff stain highlight arthroconidia
- Macrophage (early), acute inflammation/necrosis/abscess, chronic granulomatous inflammation

### TOP DIFFERENTIAL DIAGNOSES

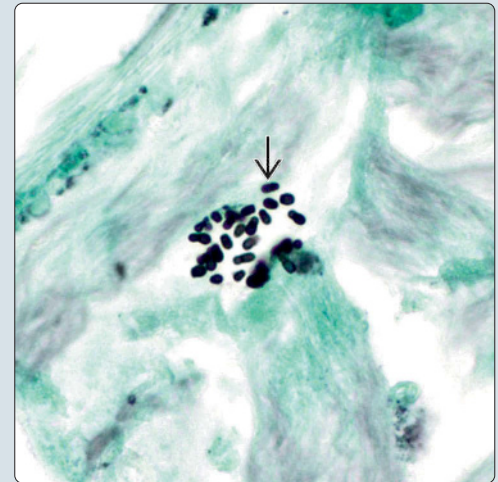
- Histoplasmosis
  - Different geographic area
- Leishmaniasis
  - *Leishmania* species are kinetoplastid parasites found within macrophages and have distinctive dot-dash (nucleus-kinetoplast) morphology

**Dense Mixed Inflammation in Disseminated *P. marneffei* Infection**

(Left) Gastrointestinal tract biopsy in disseminated *Penicillium marneffei* shows dense acute/chronic inflammation, expansion of the lamina propria, and loss of crypts. Organisms were seen on silver stain. (Right) Capsule-shaped, yeast-like arthroconidia of *P. marneffei* divide by binary fission (no budding).

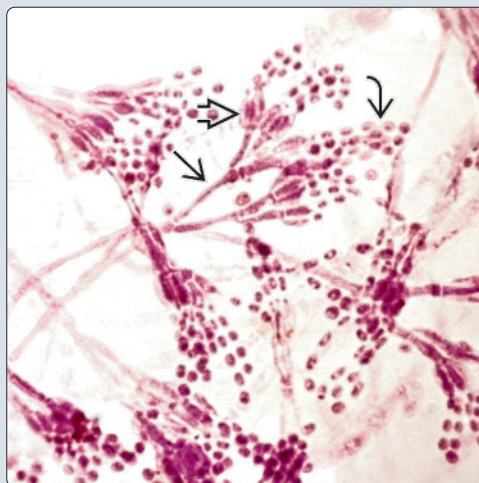


**Capsule-Shaped Yeast**



**Conidiophores With Terminal Metulae**

(Left) Cultured *Penicillium* species grown at 25°C on toluidine blue stain show conidiophores with terminal metulae, each having ~ 5 phialides, common among all species. (Right) *Penicillium* fungal culture shows powdery colonies (most species are green), which are a source of penicillin antibiotic. Reddish pigment signifies *P. marneffei*, a less common but pathogenic species.



**Powdery Colonies**





## TERMINOLOGY

### Synonyms

- *Penicillium marneffei* infection

### Definitions

- Latin: *Penicillus* (paintbrush) + Marneffe (from Hubert Marneffe, director of Pasteur Institute)

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- Environmental source is soil and rats
- Endemic in Southeast Asia
  - Patients with immunocompromise are particularly at risk for disseminated disease
  - Travel to Southeast Asia or origins in Southeast Asia for affected patients is very common and should suggest diagnosis

### Infectious Agents

- *P. marneffei*
  - Thermally dimorphic fungus (only one among *Penicillium* species) that causes localized (immunocompetent) or disseminated (immunosuppressed) disease

## CLINICAL ISSUES

### Epidemiology

- Systemic disease is almost exclusively in immunosuppressed patients, although immunocompetent may have limited localized disease
- Endemic to Indonesia, China, Vietnam, and Thailand as well as possibly in Cambodia, Laos, Myanmar, and Malaysia
  - Cases reported in Europe and United States are almost always in immunosuppressed patients with travel to endemic areas
- *Penicillium* other than *P. marneffei* have produced < 30 total cases of infection in literature

### Presentation

- Majority of skin lesions are papules with central necrotic umbilication
- Nonspecific reticuloendothelial cell infection (should highly suspect with travel history)
  - Dyspnea, cough, fever
  - Generalized lymphadenopathy, hepatosplenomegaly
  - Diarrhea
- With dissemination, skin, joints, and bone may become infected
  - Papules on face, chest, arms, and legs may occur in ~ 70% of disseminated patients
    - Appear similar to lesions of molluscum contagiosum

### Laboratory Tests

- Blood cultures from patients with disseminated disease will show hyphal forms
  - Other fluids that may be infected include urine, stool, and cerebrospinal fluid
  - 28S rRNA conserved primers with sequencing or *P. marneffei*-specific primers (with no culture available or directly on tissue)

### Treatment

- Initially amphotericin B followed by long-term itraconazole

### Prognosis

- Response to treatment is 60-80%

## MICROBIOLOGY

### Culture

- At 25-30°C, on Sabouraud dextrose agar, produces flat, powdery to velvety colonies within 3 days (rapid grower)
  - Microscopically composed of conidiophores with several metulae that end in multiple phialides
- At 35-37°C, inhibitory mould agar or brain heart infusion agar produces soft, dry, yeast-like colonies
  - Hyphal elements with fragmenting ends that produce arthroconidia (yeast-like capsules)

## MICROSCOPIC

### Histologic Features

- Organisms are ~ 5-µm capsular-shaped, yeast-like arthroconidia
  - Divide by binary fission with prominent central septa
  - Routine H&E stain may produce false capsule (confusing with *Histoplasma*)
  - Silver stains and periodic acid-Schiff stain highlight arthroconidia
- Affected tissue may have variable inflammatory reaction, depending on immunosuppressed state
  - Affected organs include skin, bone marrow, lung, gastrointestinal tract, lymph nodes, and most other organs
- Macrophages are usually present in early lesions
- Acute inflammation with necrosis may develop with frank abscesses
- Chronic inflammation produces granulomatous lesions with scarring/fibrosis without calcification

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Histoplasmosis
  - *Histoplasma capsulatum* produce small, round yeast forms, distinct halo in macrophages, reproduce by budding, and produce calcifications in chronic lesions
  - Different geographic area
    - Typically Mississippi and Ohio River valleys in USA
    - Also endemic in river valleys in Central America, South America, Africa, and Asia
      - Typically between latitudes of 45° north and 30° south
- Leishmaniasis
  - *Leishmania* species are kinetoplastid parasites found within macrophages and have distinctive dot-dash (nucleus-kinetoplast) morphology

## SELECTED REFERENCES

1. Prakit K et al: A novel inhibition ELISA for the detection and monitoring of *Penicillium marneffei* antigen in human serum. *Eur J Clin Microbiol Infect Dis*. 35(4):647-56, 2016

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## SECTION 23

# Arthropods/Parasites



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## KEY FACTS

### TERMINOLOGY

- *Demodex* is name given to small mites that live in hair follicles; condition is called demodicosis

### CLINICAL ISSUES

- Very frequently are simply incidental findings, which are unrelated to underlying pathology generating biopsy
- *Demodex* species-induced pathologic changes can cause dry eye conditions, chalazia formation, and play important role in pityriasis folliculorum
- Rosacea: Number of mites in rosacea patients higher than in control subjects

### MICROSCOPIC



- *Demodex folliculorum* adult and immature forms consume epithelial cells, cause follicular hyperplasia and marked keratinization
- *Demodex brevis* adult and immature forms consume sebaceous and meibomian gland cells when infestations are heavy

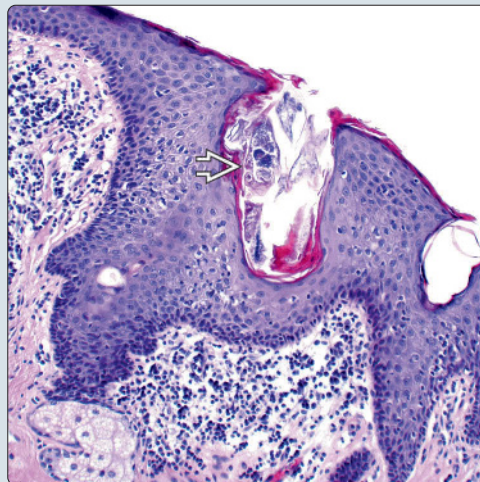
- Both mites produce inflammatory changes, epithelial hyperplasia, and follicular plugging

### TOP DIFFERENTIAL DIAGNOSES

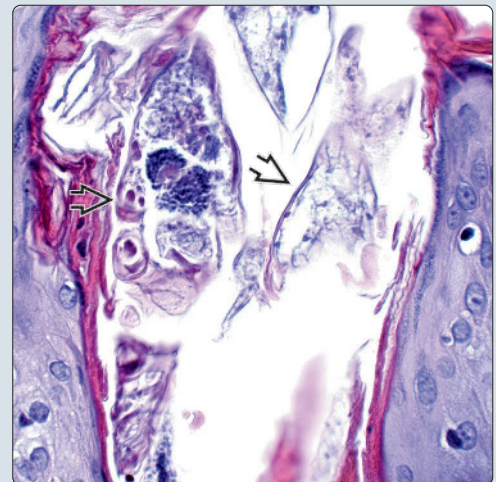
- Chalazion
  - Granulomatous inflammation of meibomian glands, composed of epithelioid cells and histocytes and chronic inflammation
  - No mites present in biopsy
- Blepharitis
  - Caused by bacterial colonization of eyelid
- Dry eye syndrome
  - Multifactorial disease of tears and ocular surface that causes discomfort and tear film instability; no mites present in histological section
- Scabies
  - Burrow through skin, not usually on face; mites in epidermis (not gland associated)
  - Mites in stratum corneum (not gland associated)

Mites in Hair Follicle



(Left) H&E-stained skin biopsy shows a dense inflammatory infiltrate around the sebaceous gland and *Demodex* mites  within the hair follicle. (Right) Hair follicle is distended with many mites in a biopsy of facial skin, consistent with *Demodex* spp. .

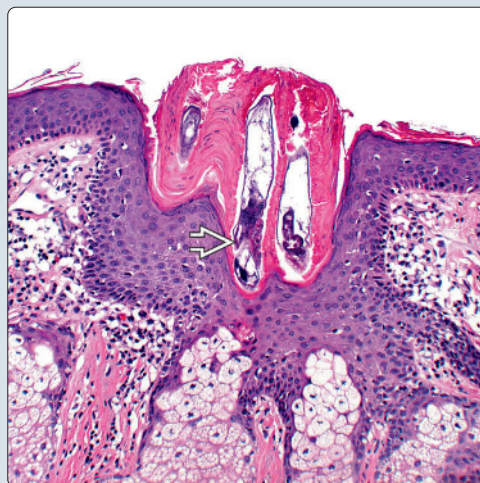


Numerous Demodex Mites, High Power

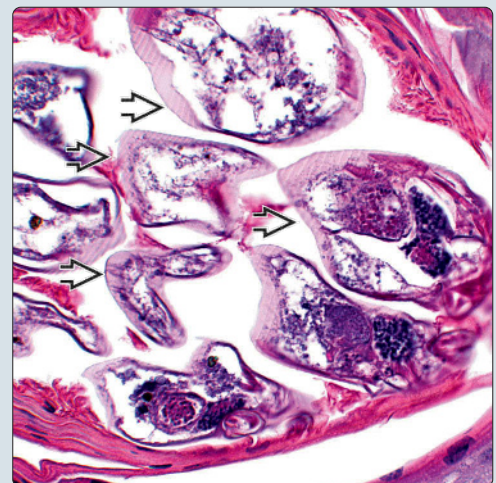


Mites With Parakeratosis

(Left) H&E section shows mild to moderate chronic inflammation around sebaceous glands. *Demodex* mites are visible  within an area of parakeratosis. (Right) Cross section of skin biopsy stained with H&E shows *Demodex* mites .



Numerous Mites in Cross Section





## TERMINOLOGY

### Synonyms

- Demodicosis
  - Demodectic mange, red mange (in canines)
- Demodicidosis

### Definitions

- Greek: "Demos" (tallow) + "dex" (woodworm)

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- Worldwide distribution, very common to find on human skin
- No racial or sex predilections have been observed

### Infectious Agents

- *Demodex* is name given to small mites that live in hair follicles; condition is called demodicosis
  - 2 species: *Demodex folliculorum* and *Demodex brevis*
    - *D. folliculorum* (all stages) is found in small hair follicles and eyelash hair follicles
    - *D. brevis* (all stages) is present in eyelash sebaceous glands, small hair sebaceous glands, and lobules of meibomian glands
  - Life cycle of *D. folliculorum* estimated to be only 14.5 days from ovum to adult stage

## CLINICAL ISSUES

### Epidemiology

- Prevalence of *Demodex* spp. infestation in 1 recent study was 41% and was highest among inpatients and elderly
- In general population, age 20-30 has highest colonization due to rate of sebum production

### Presentation

- Very frequently are simply incidental findings, which are unrelated to underlying pathology generating biopsy
- Demodicidosis
  - Pruritic, erythematous, papulopustular lesions
  - Variations include pityriasis folliculorum, rosacea-like demodicidosis, or demodicidosis gravis
- Madarosis (loss of lashes) is associated with heavy infestation by mites
  - *Demodex* species-induced pathologic changes can cause dry eye conditions and chalazia formation
- *Demodex* blepharitis
  - Ocular irritation, itching, and scaling of lids
- Rosacea
  - Number of *Demodex* mites in rosacea patients higher than in control subjects
- *Demodex* can proliferate in immunodeficiency states such as HIV infection

### Treatment

- Tea tree oil with *Macadamia* nut oil are commonly used
- Topical insecticides in heavy infestation
- Oral ivermectin in severe cases, e.g., HIV patients

### Prognosis

- No major morbidity or mortality

## MACROSCOPIC

### General Features

- *D. folliculorum* measures 0.3-0.4 mm in length, whereas *D. brevis* measures 0.15-0.2 mm with similar structure of head and thorax but shorter abdomen

## MICROSCOPIC

### Histologic Features

- Demodicidosis show papulopustular lesions with neutrophils in/around glands with organisms
- *D. folliculorum* adult and immature forms consume epithelial cells and cause follicular hyperplasia and marked keratinization
- *D. brevis* adult and immature forms consume sebaceous and meibomian gland cells when infestations are heavy
- Both mites produce inflammatory changes, epithelial hyperplasia, and follicular plugging
- Organisms are mites and have chitin exoskeleton

## DIFFERENTIAL DIAGNOSIS

### Chalazion

- Granulomatous inflammation of meibomian glands, composed of epithelioid cells and histocytes and chronic inflammation; no mites present in biopsy
- Demodicidosis should be considered in adults presenting with recurrent chalazia

### Blepharitis

- Caused by bacterial colonization of eyelid

### Dry Eye Syndrome

- Multifactorial disease of tears and ocular surface that causes discomfort and tear film instability; no mites present in histological section

### Scabies

- Burrow through skin, not usually on face; mites in epidermis (not gland associated)

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## KEY FACTS

### ETIOLOGY/PATHOGENESIS

- Insect bites: Venoms and saliva of mosquitos, flies, ants, fleas, lice, and other insects
- Tick bites: *Amblyomma*, *Dermacentor*, *Rhipicephalus*, and *Ixodes* ticks are common species
- Spider bites: Commonly brown recluse (*Loxosceles reclusa*) spiders

### CLINICAL ISSUES

- Insect bites: Most commonly present with excoriated purpuric papules but may present with bullae, nodules, and ulcers
- Tick bites: Typically presents with tick still attached
- Brown recluse spider bites: Red, white, and blue sign

### MICROSCOPIC

- Insect bites: Various degrees of spongiosis, dermal edema, and wedge-shaped perivascular lymphocytic infiltrate with eosinophils

- Tick bites: Mouth parts may be seen in dermis with dense mixed cell infiltrate
- Spider bites: "Mummified" coagulative necrosis with dense neutrophilic infiltrate ± vasculitis

### DIAGNOSTIC CHECKLIST

- Insect bites
  - Be aware of vector-borne diseases, which are occasionally transmitted by flies or fleas
  - Be aware of exaggerated bite reactions in patients with chronic lymphocytic leukemia, HIV, and mantle cell lymphoma
- Tick bites
  - Be aware of various tick-borne systemic diseases: Quite rare (only 1-2% of all tick bites) and does not happen until after 1st 24 hours of attachment
- Brown recluse spider bite
  - Dark violin shape is located on top of leg attachment region of brown recluse spider

Arthropod Bite



Clinical features vary depending on the arthropod species and their venom. Most commonly, lesions appear as excoriated purpuric papules [2], but vesicles, bullae, nodules, erosions, and ulcers can also occur.



## TERMINOLOGY

### Synonyms

- Arthropod assault, insect bite, tick bite, spider bite, papular urticaria

### Definitions

- Reaction caused by wound, venom, or saliva received from mouth of arthropod or animal

## ETIOLOGY/PATHOGENESIS

### Insect (Insecta) Bites

- Insect venoms and saliva of mosquitos, flies, ants, fleas, lice, and other insects
- Immediate reactions are related to histamine, serotonin, formic acid, and kinin
- 1/4 of reported cases of anaphylaxis are related to type I allergic reaction to venoms of Hymenoptera (bees and wasps)
- Vector-borne diseases, such as cat scratch disease, bacillary angiomatosis, tularemia, and spotted fever, are occasionally transmitted by flies or fleas

### Tick (Acarina) Bites

- Ticks are ectoparasites, living by hematophagy on blood of mammals and birds
  - *Amblyomma*, *Dermacentor*, *Rhipicephalus*, and *Ixodes* ticks are common species
- Hypersensitivity reactions at attachment site
  - May present as erythematous papule, plaque, nodule, vesicle, or bulla
  - Mouth parts of arthropod may become imbedded in skin, resulting in local erythematous papule or persistent granulomatous nodule
- Important disease vectors for various tick-borne systemic diseases
  - Transmission quite rare, with only 1-2% of tick bites resulting in tick-borne disease
  - Transmission does not happen until after 1st 24 hours of attachment

### Spider (Araneae) Bites

- Brown recluse (*Loxosceles reclusa*) spiders
  - Sphingomyelinase D is major toxin in venom, interacting with serum amyloid protein
    - Results in ulcers and necrotic eschars
  - Hyaluronidase induces spreading of eschars
  - Geographically found in south central United States

## CLINICAL ISSUES

### Presentation

- Insect bites
  - Clinical features vary depending on arthropod species and their venom
    - Excoriated purpuric papules most common
    - Other features include vesicle, bulla, nodule, erosion, and ulcer
    - Rare systemic features include anaphylaxis by Hymenoptera stings
- Tick bites

- Patients typically present with tick still attached (commonly on scalp and occasionally on neck and upper trunk)
- After tick is removed, hypersensitivity reactions commonly misinterpreted as erythema migrans
  - Erythematous pruritic papule, plaque, nodule, vesicle, and bulla at attachment site
- Important disease vectors for spotted fever, relapsing fever, Colorado tick fever, Q fever, tularemia, bacillary angiomatosis (rare), Lyme disease, ehrlichiosis, babesiosis, and meningoencephalitis
- Spider bites
  - Brown recluse spider bites
    - Necrotic eschar or ulceration, surrounded by pale then erythematous patches: Red, white, and blue sign
    - Systemic symptoms such as disseminated intravascular coagulation, Coombs-positive hemolytic anemia, airway obstruction, and shock may occur

### Treatment

- Insect bites
  - Topical antipruritic agents
  - Topical corticosteroids
  - For persistent cases, intralesional corticosteroid (e.g., triamcinolone) injection
  - Prevention
    - DEET (N, N-diethyl-3-methylbenzamide) applied to skin
  - Allergic patient who experienced anaphylaxis by sting should carry epinephrine auto injector
  - Patients with exaggerated insect bites successfully treated with dapsone
- Tick bites
  - Tick removal
    - Plastic tick removal devices are available
    - Petroleum jelly, fingernail polish, isopropyl alcohol, and hot matches are ineffective
    - If mouth or head part of removed tick is missing, punch excision may be required
  - Prevention
    - Permethrin applied to clothing
    - DEET to skin
  - Tick-borne diseases
    - Treatment varies by disease, although most tick-borne diseases are treated with doxycycline
- Spider bites
  - Brown recluse spider bites
    - Rest, ice, and elevation
    - Oral or intravenous corticosteroid for systemic symptoms
    - Pain relief by antiinflammatory drugs
    - Tetanus immunization may be applied

### Prognosis

- Insect bites
  - Excellent in most cases
  - Anaphylaxis may cause death if not properly treated
- Tick bites
  - Excellent in most cases if tick removed properly
  - Mortality rate is 10% in patients with tick paralysis
- Spider bites

# Bite Reactions

- o Brown recluse spider bites
  - Over several days, patient develops necrotic eschars that may heal by secondary intention or require surgical treatment
  - Systemic symptoms may cause death

## MACROSCOPIC

### General Features

- Insect bites
  - o Erythematous papules, vesicles, bullae, nodules, erosions, and ulcers
- Tick bites
  - o Tick attached to scalp or elsewhere on upper part of body
  - o Erythematous papule, plaque, nodule, vesicle, or bulla at attachment site after tick removed
- Spider bites
  - o Brown recluse spider bite
    - Dry necrotic eschar or ulceration, surrounded by pale then erythematous patches

## MICROSCOPIC

### Histologic Features

- Insect bites
  - o Prominent papillary dermal edema
  - o Spongiosis ± epidermal necrosis or intraepidermal blister formation
  - o Wedge-shaped perivascular lymphocytic infiltrate with eosinophils
  - o Variable vascular damage
  - o Variable atypical lymphocytes
  - o Chronic lesion may reveal pseudoepitheliomatous hyperplasia ± atypical dense lymphocytic infiltrate, mimicking malignant lymphoma
  - o Exaggerated bite reaction
    - Eosinophilic spongiosis, vesiculation, and full-thickness necrosis
    - Superficial and deep perivascular and interstitial infiltrates of lymphocytes and eosinophils
    - Flame figures, lymphocytic vasculitis, and lymphoid nodules may be present
- Tick bites
  - o Acute lesions
    - Intradermal cavity, below which mouth parts may be seen
    - Tract of necrosis on either side
    - Fibrin thrombi may be seen in dermal capillaries
    - Moderately dense perivascular mixed cell infiltrate of neutrophils, lymphocytes, plasma cells, histiocytes, and eosinophils
  - o Chronic lesions
    - Diffuse superficial and deep mixed cell infiltrate of fewer neutrophils and more lymphocytes
    - Cutaneous lymphoid hyperplasia may be seen
    - Occasional giant cells, dermal fibrosis, and granuloma formation
- Spider bites (brown recluse bite)
  - o Early stage
    - Neutrophilic infiltrate

- o Middle stage
  - "Mummified" coagulative necrosis in epidermis and dermis
  - Neutrophilic, band-like infiltrate around edge of eschar
  - Large vessel vasculitis may be seen
- o Late stage
  - Total skin necrosis

## DIFFERENTIAL DIAGNOSIS

### Insect Bites

- Allergic contact dermatitis
  - o Clinically, easy to distinguish; histologically, could be similar
- Lymphoma
  - o In pseudolymphomatous bite reaction, expect to see less cell atypicality and occasional formation of lymphoid follicles

### Tick Bites

- Gyrate erythema
  - o Negative ELISA test for Lyme disease; no retention of sting apparatus
- Cellulitis
  - o Diffuse; no retention of sting apparatus; no tract of necrosis

### Brown Recluse Spider Bites

- Necrotizing fascitis
  - o Clumps of gram-positive bacteria and positive bacterial culture
- Cellulitis
  - o Necrosis is uncommon; no vasculitis

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Insect bites: Most commonly present with excoriated purpuric papules but may present with bullae, nodules, and ulcers
- Tick bites: Typically present with tick still attached
- Brown recluse spider bites: Red, white, and blue sign

### Pathologic Interpretation Pearls

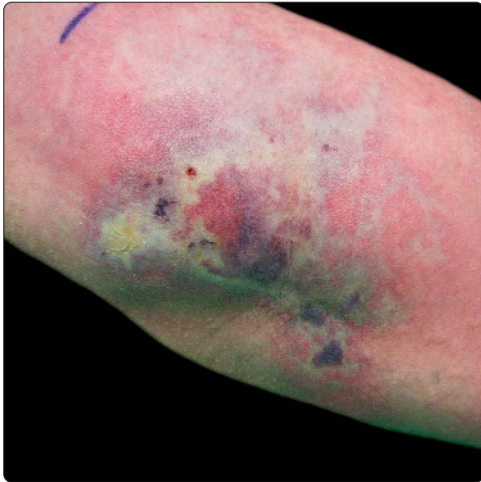
- Insect bites: Various degrees of spongiosis, dermal edema, and wedge-shaped perivascular lymphocytic infiltrate with eosinophils
- Tick bites: Moderately dense mixed cell infiltrate, intradermal cavity, and often mouth parts beneath
- Brown recluse bites: Diffuse, "mummified," coagulative necrosis with dense neutrophilic infiltrate ± leukocytoclastic vasculitis

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2. Singh S et al: Insect bite reactions. *Indian J Dermatol Venereol Leprol.* 79(2):151-64, 2013
3. Haddad V Jr et al: Tropical dermatology: Venomous arthropods and human skin: Part II. Diplopoda, Chilopoda, and Arachnida. *J Am Acad Dermatol.* 67(3):347.e1-9; quiz 355, 2012
4. Haddad V Jr et al: Tropical dermatology: Venomous arthropods and human skin: Part I. Insecta. *J Am Acad Dermatol.* 67(3):331.e1-14; quiz 345, 2012



**Brown Recluse Spider Bite**



**Dermacentor Variabilis Tick**

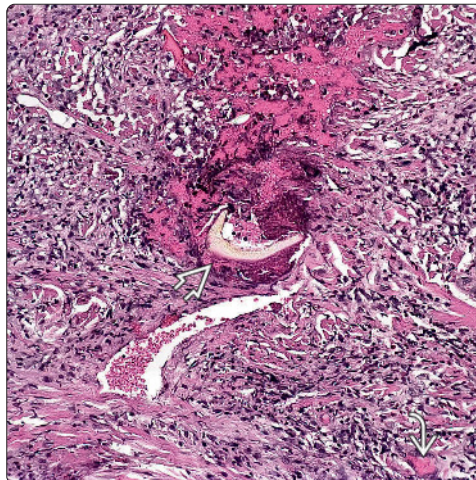


(Left) The red, white, and blue sign is shown in a brown recluse spider bite. The sign is identified by dry necrotic eschar or ulceration, surrounded by pale then erythematous patches. (Right) A male *Dermacentor variabilis* tick (American dog tick) is shown. Other common species include *Amblyomma maculatum*, *A. americanum*, *D. andersoni*, *Rhipicephalus sanguineus*, *Ixodes scapularis*, and *I. pacificus*.

**Tick Histology**

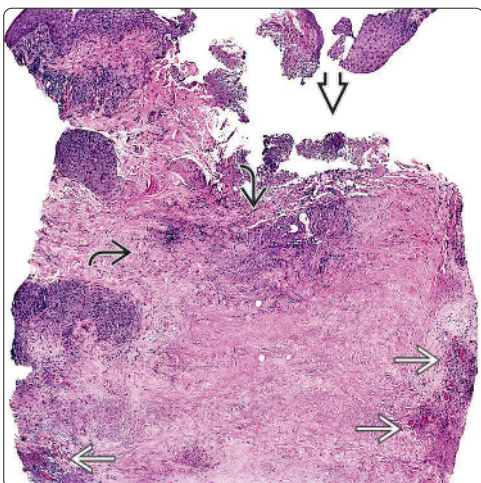


**Tick Mouth Parts**

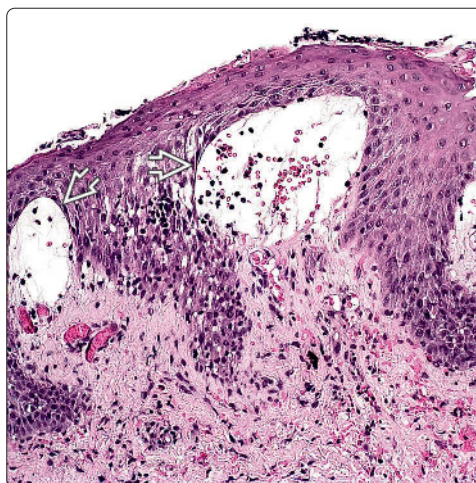


(Left) A tick attached to the skin is shown. Moderately dense perivascular mixed cell infiltrate is seen. An intradermal cavity and necrosis are also visible, below which mouth parts may be seen. (Right) A chronic bite lesion shows mouth parts of the tick in the intradermal necrotic tract, surrounded by dense, diffuse, superficial and deep mixed cell infiltrate of fewer neutrophils and more lymphocytes. Fibrin thrombi may be seen in dermal capillaries.

**Necrosis and Thrombosis**



**Intraepidermal Blister From Spongiosis**



(Left) The ulcer and coagulative necrosis in the epidermis and dermis, as well as neutrophilic, band-like infiltrate around the edge of the eschar/ulcer, are shown. Note thrombosed blood vessels from vasculitis. (Right) Spongiosis, intraepidermal blister formation, and prominent papillary dermal edema may be seen. Wedge-shaped, perivascular, moderate to dense lymphocytic infiltrate with eosinophils is typical.



## KEY FACTS

### ETIOLOGY/PATHOGENESIS

- Caused in humans by scabies mite *Sarcoptes scabiei* variety *hominis*

### CLINICAL ISSUES

- Predilection for interdigital areas and flexures, waist, ankles, and intergluteal fold
- 3 different clinical forms
  - Papulovesicular lesions
  - Persistent nodules
  - Norwegian (crusted or keratotic) scabies

### MICROSCOPIC

- Diagnostic finding is presence of mite, feces, or eggs in stratum corneum
  - Many levels may be necessary
- Superficial and deep infiltrate of lymphocytes, histiocytes, mast cells, and eosinophils

- Clue to diagnosis is presence of egg case remnants, which appear similar to pigtails
- In KOH prep, mite looks flattened and has oval body showing wrinkle-like corrugations

### TOP DIFFERENTIAL DIAGNOSES

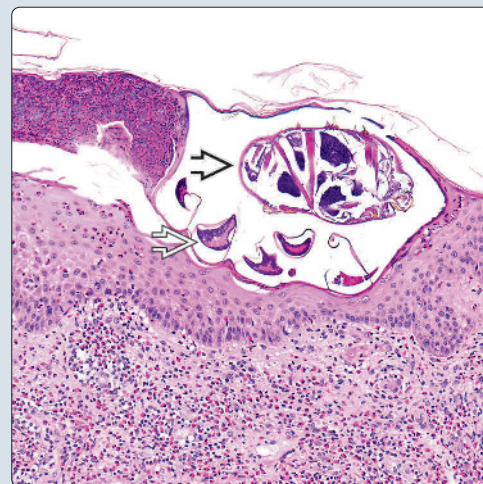
- Dermal hypersensitivity reactions
  - Clinical correlation or histologic identification of scabietic parts is needed to correctly decipher
- Lymphomatoid papulosis
  - Clinical correlation: Crops of papules on abdomen, chest, back, arms, and legs and spontaneous resolution in 2-8 weeks favor LyP
- Lymphocytoma cutis
  - Usually is single nodule 1-3 cm in diameter

**Excoriated Papules and Burrows**

(Left) Scabies presented in this patient as multiple, excoriated papules and burrows on the hand. (Right) This histologic section shows eggshells and a scabietic mite burrowed in the cornified layer with a dense, dermal, eosinophilic, inflammatory infiltrate. (Courtesy UCSF Dermatopathology Service.)

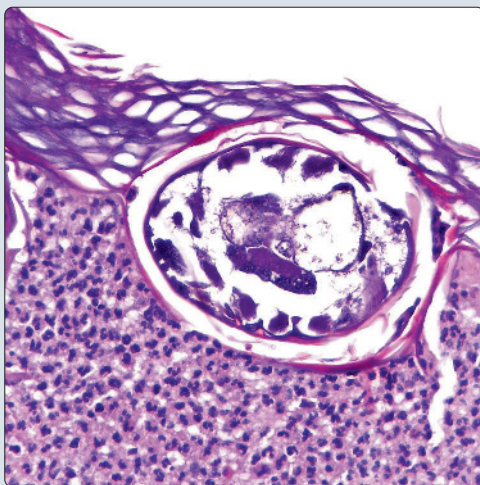


**Eggshells and Mite in Stratum Corneum**

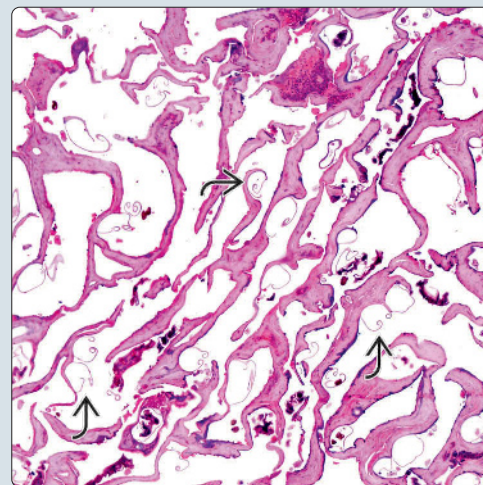


**Mite Overlying Pustule in Stratum Corneum**

(Left) This biopsy specimen of scabies demonstrates a scabietic mite overlying a pustule of neutrophils. (Right) Norwegian (crusted or keratotic) scabies demonstrates massive orthokeratosis with multiple egg case remnants that resemble pigtails. (Courtesy A. Bowen, MD.)



**Pigtails Within Massive Orthokeratosis**





**TERMINOLOGY****Synonyms**

- Itch mite infestation, 7-yr itch

**Definitions**

- Ectoparasitic infestation with about 300 million cases worldwide each yr
  - Common predisposing factors are overcrowding, immigration, poor hygiene, poor nutritional status, homelessness, dementia, and sexual contact
  - Direct skin-to-skin contact for 15-20 min needed to transfer mites from one person to another
  - Prevalence higher in children and sexually active adults

**ETIOLOGY/PATHOGENESIS****Infectious Agents**

- Caused in humans by scabies mite *Sarcoptes scabiei* variety *hominis*
- Highly host specific
- 30-day lifecycle is completed within epidermis
  - Female deposits 60-90 eggs, which require 10 days to mature

**CLINICAL ISSUES****Presentation**

- History, type, distribution of lesion (symmetrical), and pruritus are basis for clinical diagnosis
  - Burrows (linear superficial lesions) are diagnostic
  - Predilection for interdigital areas and flexures, waist, ankles, and intergluteal folds
  - In infants, lesions are more generalized (feet, scalp, and face)
- 3 different clinical forms
  - Papulovesicular lesions
    - Papules and papulovesicles are intensely pruritic
    - Fine, wavy, dark lines that represent excreta-soiled burrows in horny layer with vesicle at end
  - Persistent nodules
    - Usually in children and young adults: Reddish-brown pruritic nodules on thighs, scrotum, and trunk
  - Norwegian (crusted or keratotic) scabies
    - Widespread crusted and hyperkeratotic lesions
    - Usually seen in immunodeficient patients or patients with Down syndrome

**Treatment**

- Most commonly used treatment modalities are topical permethrin and oral ivermectin

**Prognosis**

- Persistence of symptoms for 2-6 weeks after successful treatment is common
- Most recurrences due to reinfection from untreated contacts

**MICROSCOPIC****Histologic Features**

- Papulovesicular lesions

- Diagnostic finding is presence of mite, feces (scybala), or eggs in stratum corneum (many levels may be necessary)
  - Sometimes mite itself is not seen
  - Clue to diagnosis is presence of egg case remnants, which appear similar to pigtailed
- Superficial and deep infiltrate of lymphocytes, histiocytes, mast cells, and eosinophils
- Spongiotic foci and spongiotic vesicles within epidermis, with exocytosis of eosinophils and sometimes neutrophils
- Persistent nodular scabies
  - Dense superficial and deep inflammatory cell infiltrate with lymphocytes, macrophages, plasma cells, eosinophils, Langerhans cells
  - Sometimes lymphoid follicles and extension to subcutaneous fat
  - Mite parts seen in ~ 20% of cases in serial sections
- Norwegian scabies
  - Massive orthokeratosis and parakeratosis with mites in all stages
  - Epidermis: Psoriasiform hyperplasia, focal spongiosis, exocytosis of neutrophils and eosinophils
  - Sometimes intraepidermal microabscesses
  - Dermis with superficial and deep infiltrate of chronic inflammatory cells with interstitial eosinophils

**Cytologic Features**

- In KOH prep, mite looks flattened and has oval body showing wrinkle-like corrugations
  - 8 short legs; sometimes eggs can be seen within abdomen
  - Usual size of mite: 0.35 x 0.3 mm

**DIFFERENTIAL DIAGNOSIS****Dermal Hypersensitivity Reactions**

- Dermal infiltrate in scabies is similar to dermal hypersensitivity reactions, such as urticaria or drug eruptions
- Clinical correlation or histologic identification of scabetic parts is needed to correctly decipher

**Lymphomatoid Papulosis (LyP)**

- In long duration of scabies infestation (> 3 months), CD30(+) cells are increased in inflammatory infiltrate, similar to infiltrates of LyP
- Clinically, LyP may be mildly itchy (vs. intense pruritus with scabies)
- Clinical correlation: Crops of papules on abdomen, chest, back, arms, and legs and spontaneous resolution in 2-8 weeks favor LyP

**Lymphocytoma Cutis**

- Can mimic persistent nodular scabies histologically with slightly atypical-looking lymphocytes
- Clinicopathologic correlation is important
  - Usually is single nodule 1-3 cm in diameter

**SELECTED REFERENCES**

1. Elwood H et al: Superficial fibrin thrombi ... and other findings: a review of the histopathology of human scabetic infections. *J Cutan Pathol*. 42(5):346-52, 2015

## Leishmaniasis

## KEY FACTS

## ETIOLOGY/PATHOGENESIS

- Identification of kinetoplast allows for distinction from other commonly confused microorganisms

## CLINICAL ISSUES

- 4 main types of clinical disease seen
  - Cutaneous, diffuse cutaneous, mucocutaneous, and visceral leishmaniasis
  - Different species of *Leishmania* cause different clinical diseases
- Mucocutaneous leishmaniasis is most serious
  - May form midline destructive lesion with mutilation of nose or entire nasolabial area

## MICROSCOPIC

- Oval-shaped, 2-4  $\mu\text{m}$  amastigotes can be seen in periphery of histiocytes, especially in clear spaces
- Organisms with eccentric nucleus and kinetoplast at opposite pole are good clues to diagnosis

- Marquee sign is peripheral localization of parasites (amastigotes) within histiocytes
- When many microorganisms are present, diagnosis is easy
  - Higher level of certainty is needed when organisms are scarce

## ANCILLARY TESTS

- Gram stain, Giemsa, Brown-Hopps, or Leishmanin (G2D10) antibody stains are most commonly used
- Immunohistochemical stains to identify amastigotes
- Giemsa-stained touch preparations may be helpful in identifying free amastigotes

## TOP DIFFERENTIAL DIAGNOSES

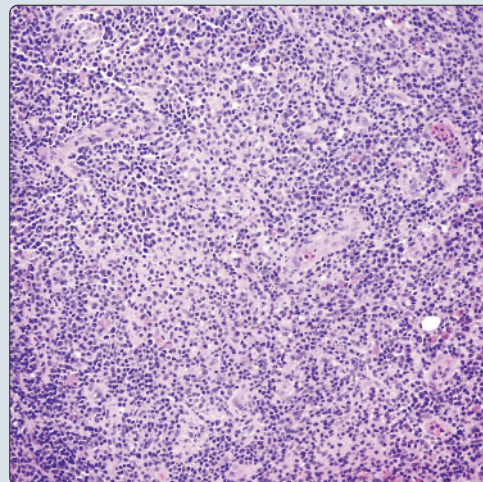
- Histoplasmosis
- Rhinoscleroma
- Granuloma inguinale
- Malakoplakia

Well-Demarcated Ulcer With Elevated Border

(Left) This is cutaneous leishmaniasis involving the arm. Note the well-demarcated, elevated border of the lesion surrounding the central ulcer resembling a pizza pie. (Right) This low-power view of acute leishmaniasis demonstrates a diffuse dermal infiltrate of chronic inflammatory cells (the epidermis had ulcerated off). Any biopsy that shows this degree of inflammation warrants careful searching for an infectious organism.

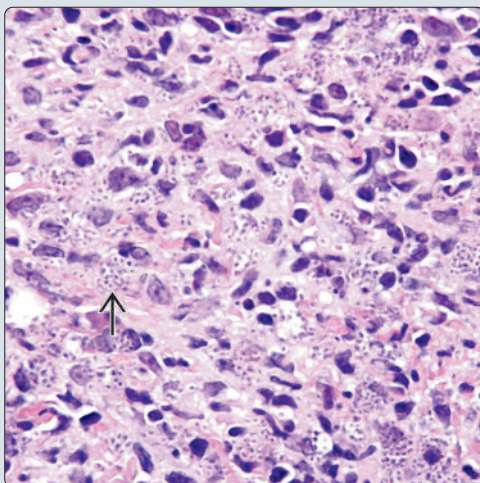


Acute Leishmaniasis With Diffuse Dermal Inflammation



Numerous Amastigotes Within Histiocytes

(Left) This lesion of cutaneous leishmaniasis demonstrates numerous amastigotes within the cytoplasm of numerous histiocytes that filled the dermis. (Right) Cutaneous leishmaniasis manifests as a typical round to oval, painless ulcer on an exposed area of skin with a well-delineated elevated border. This patient spent 3 months in Peru and did not recall a bite. (Courtesy T. Sofarelli, PA-C.)



Well-Demarcated Ulcer With Raised Border Resembling Pizza Pie





## TERMINOLOGY

### Synonyms

- Cutaneous leishmaniasis
  - Oriental sore (Asia), uta (Andes), chiklero ulcer (Mexico, typically involves ear), tropical sore, Bagdad boil, Bauer ulcer, Delhi boil, Aleppo boil, Aleppo button
- Mucocutaneous leishmaniasis
  - American leishmaniasis, espundia (Amazon basin), pian bois (northern Brazil), forest yaws
- Visceral leishmaniasis
  - Kala-azar, black fever, dumdum fever

### Definitions

- Protozoal infection caused by intracellular parasites of *Leishmania* genera of Trypanosomatidae family
- Old World leishmaniasis is caused by species located in India, Mediterranean, Middle East, Africa, and Asia (mainly causes cutaneous and visceral disease)
- New World leishmaniasis is caused by species in Central and South America (causes cutaneous, mucocutaneous, and visceral disease)

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- Disease transmitted by animal reservoirs (dogs or rodents) to humans by bite of female sandfly (genera *Phlebotomus* and *Lutzomyia*)
- Parasite has 2 different forms: Promastigote and amastigote
- **Amastigote** or nonflagellated form is seen in human tissue
  - Ovoid in shape
  - Measures 3-5 µm in diameter
  - Contains nucleus and kinetoplast
    - Kinetoplast is unique form of mitochondrial DNA
    - Identification of **kinetoplast** allows for distinction from other commonly confused microorganisms

### Infectious Agents

- Caused by several species of *Leishmania* and divided into 4 main groups or complexes
  - *Leishmania tropica* complex
    - Includes *L. tropica*, *Leishmania major*, and *Leishmania aethiopica*
  - *Leishmania mexicana* complex
    - Includes *L. mexicana*, *Leishmania amazonensis*, and *Leishmania pifanoi*
  - *Leishmania braziliensis* complex
    - Includes *L. braziliensis*, *Leishmania peruviana*, *Leishmania panamensis*, and *Leishmania guyanensis*
  - *Leishmania donovani* complex
    - Includes *L. donovani*, *Leishmania infantum*, and *Leishmania chagasi*
  - Complexes 1-3 cause cutaneous leishmaniasis
  - Complex 3 causes mucocutaneous leishmaniasis
  - Complex 4 causes visceral leishmaniasis

## CLINICAL ISSUES

### Epidemiology

- Incidence

- Worldwide
  - ~ 1.5 million new cases of cutaneous leishmaniasis/year
  - Occurs in Mexico, Central and South America (except Uruguay and Chile), Southern Europe, Asia, Middle East, and Africa
- In USA
  - Rare cutaneous case reports in southern Texas

### Presentation

- 4 main clinical presentations: Cutaneous, mucocutaneous, visceral, diffuse cutaneous
- **Cutaneous leishmaniasis** appears 10-90 days following sandfly bite
  - Lesions are generally limited only to areas of skin exposed to insects
    - Face, neck, extremities, etc.
  - Initially occurs as solitary papule and then forms ulcer with raised border
  - Lesions can occasionally be multiple
  - Lesions may take on sarcoidal or verrucous appearance
    - 10% will have lymphadenopathy, and lesions may take on sporotrichoid pattern following lines of lymphatic drainage
- **Mucocutaneous leishmaniasis**
  - Caused by species of *L. braziliensis* complex
  - After dormant period (months to years) can hematogenously disseminate and
    - Cause ulceration of mucosa or nasal septum
    - May form midline destructive lesion with mutilation of nose or entire nasolabial area
    - May progress to destruction of palate
- **Visceral leishmaniasis**
  - Caused by species of *L. donovani* complex
  - Systemic disease with fever, hepatosplenomegaly, lymphadenopathy, skin involvement, weight loss, and secondary infections
  - Can be fatal if left untreated
  - **Post-kala-azar** is more severe form with skin lesions appearing as macules or nodules
- **Diffuse cutaneous leishmaniasis**
  - Rarely seen
  - Due to lack of patient's inability to attack microorganism
    - Similar to lepromatous leprosy and may clinically be confused with this entity
  - Caused by *L. mexicana*, *L. amazonensis*, and, more rarely, *L. braziliensis* and *L. aethiopica*
  - Multiple organisms will be seen in macrophages
  - Lesions will not ulcerate and will consist of multiple large nodules over entire body

### Treatment

- Options, risks, complications
  - **Old World leishmaniasis** often spontaneously resolves, so treatment is often not needed
    - When treatment is indicated, antimonials, cryotherapy, ketoconazole, or paromomycin can be used
  - **New World** or **American leishmaniasis** carries risk of mucocutaneous disease, so treatment is always recommended

- Antimonials such as N-methylglucamine and sodium stibogluconate are drugs of choice
- Cardiac and renal toxicity are possible complications of antimonial therapy
- Other options include amphotericin-B, pentamidine, or miltefosine

## MACROSCOPIC

### Sections to Be Submitted

- Multiple biopsies from edge of lesion are recommended for optimal chance of identification in tissue specimens
- Scrapings from base of lesion can be smeared on slide and stained with Giemsa to help identify organisms

## MICROSCOPIC

### Histologic Features

- When many microorganisms are present, diagnosis is easy
  - Higher level of certainty is needed when organisms are scarce
- Acute lesions
  - Usually have papillary dermal edema, with many histiocytes in edematous areas
    - Best area to look for organisms
  - Often show diffuse dermal infiltrate of chronic inflammatory cells, including lymphocytes, histiocytes, plasma cells, and occasionally eosinophils
  - Round to oval, 2- to 4- $\mu$ m amastigotes can be seen in periphery of histiocytes, especially in clear spaces
    - Marquee sign is peripheral localization of parasites (amastigotes) within histiocytes
    - Identification of nucleus and (if possible) kinetoplast is diagnostic
    - Identification of individual species requires PCR and cannot be determined in tissue sections
  - Epidermis is often ulcerated, but can also show acanthosis and hyperkeratosis
- Chronic lesions
  - Show tuberculoid granulomas with persistent mild to moderate chronic inflammatory infiltrate
    - Granulomas are superficial and deep, and occasionally have central necrosis, mimicking tuberculosis
  - Will often show fewer parasitic organisms
  - Often numerous plasma cells and occasionally multinucleate giant cells are present
  - Pseudoepitheliomatous hyperplasia may be seen in longstanding lesions

## ANCILLARY TESTS

### Cytology

- Giemsa-stained direct smears may be helpful in identifying free amastigotes
  - Identification of nucleus and, if possible, kinetoplast of amastigotes is best way to diagnose disease

### PCR

- Can detect down to 0.14 mg of total leishmania DNA
- This molecular test has now been simplified down to OligoC-Test that is simple, rapid, and standardized
- Currently available in countries with high incidence

## Special Stains and Immunohistochemistry

- Several stains can be performed to help identify or highlight phagocytized parasites
  - Gram, Giemsa, Brown-Hopps, or Leishman (G2D10) antibody stains are most commonly used
    - Can be done on touch preps, aspirations, or tissue sections
- Several studies have compared diagnosis using touch preps (skin smears) and immunohistochemically stained tissue sections
  - Immunohistochemically stained slides appear to be slightly more sensitive than Giemsa-stained touch preparations

## DIFFERENTIAL DIAGNOSIS

### Histoplasmosis

- Round (leishmaniasis is more oval)
- Similar size and location in histiocytes
- Marquee sign can also be seen in histoplasmosis (termed Chicago wheel)
- PAS or GMS stain to highlight fungi
  - *Histoplasma capsulatum* will contain pseudocapsule, whereas *Leishmania* parasites lack capsule
- No history of travel to endemic area of leishmaniasis and history of travel to states bordering Ohio river valley or lower Mississippi in USA
  - Cutaneous leishmaniasis is only found in USA in southernmost portion of Texas

### Rhinoscleroma

- Causative organism *Klebsiella rhinoscleromatis* may be seen in macrophages
  - Organisms are bacilli and rod-shaped, not oval like leishmaniasis
- Numerous Mikulicz cells (macrophages with vacuolated cytoplasm) often with organisms inside
- Numerous prominent plasma cells and Russell bodies

### Granuloma Inguinale

- Disease often limited to external genitalia
- Often see neutrophilic microabscesses
- Causative organism *Calymmatobacterium granulomatis* can be seen within macrophages
  - Organisms are bacilli and rod-shaped, similar to *K. rhinoscleromatis*

### Malakoplakia

- More commonly infection of bladder, but skin involvement has been reported
- Characteristic finding is von Hansemann cells [PAS(+), diastase-resistant inclusions within macrophages]
- Other characteristic findings (Michaelis-Gutmann bodies) are 5- to 15- $\mu$ m ovoid to round basophilic inclusions in large histiocytes
- Gram stain may reveal gram-negative bacteria within histiocytes

## SELECTED REFERENCES

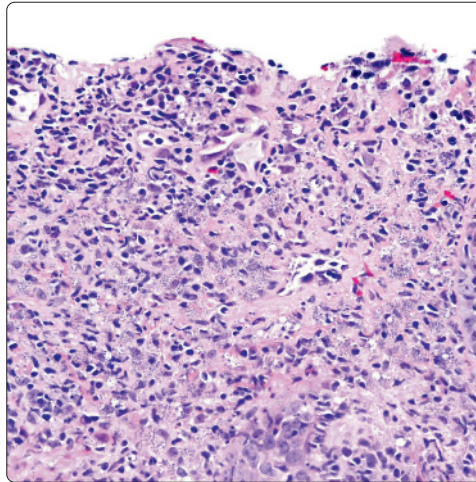
1. Kevric I et al: New World and Old World Leishmania Infections: A Practical Review. *Dermatol Clin*. 33(3):579-93, 2015



**Characteristic, Destructive Mucocutaneous Lesion**

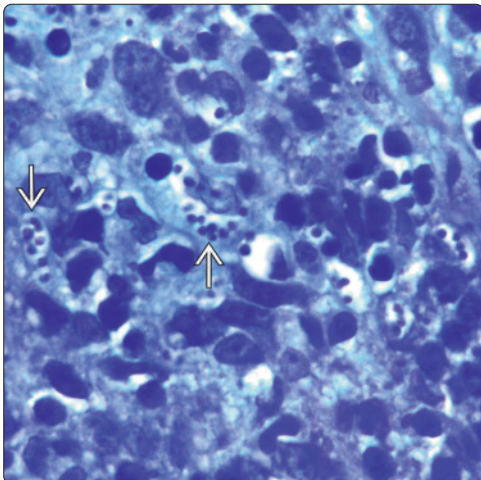


**Ulcerated Epidermis With Diffuse Dermal Inflammatory Infiltrate**

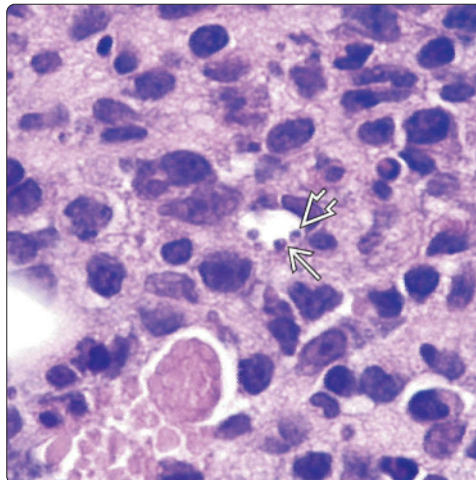


**(Left)** Clinical photograph shows mucocutaneous leishmaniasis. Involvement of the mucous membranes is notorious for producing destructive lesions, sometimes mutilating the face and eroding the nasal septum. **(Right)** This biopsy of leishmaniasis demonstrates an ulcerated epidermis with a diffuse dermal infiltrate of chronic inflammatory cells. Any biopsy that shows this degree of inflammation warrants careful searching on higher power for an infectious organism.

**Amastigotes Within Histiocytes Highlighted With Giemsa Stain**

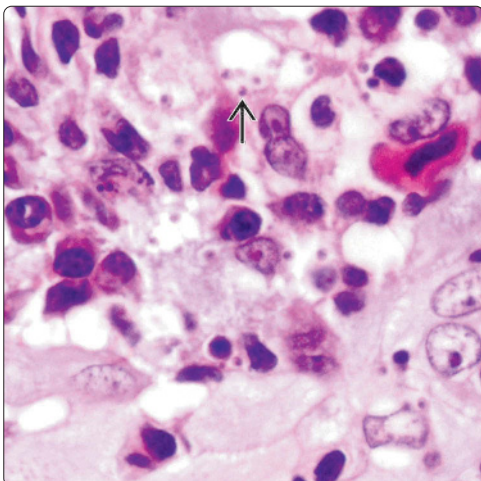


**Peripheralization of Amastigotes Within Histiocytes Yielding Marquee Sign**

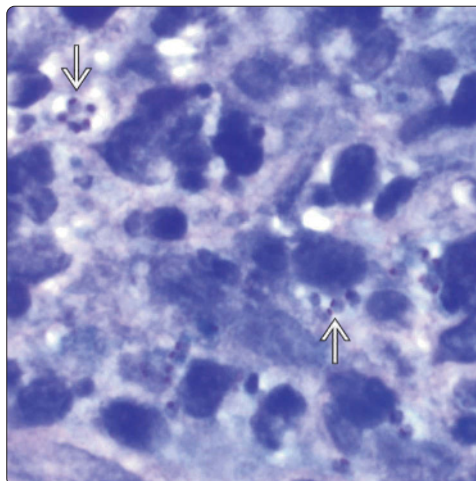


**(Left)** Giemsa stain demonstrates multiple amastigotes within the cytoplasm of histiocytes. Although hard to appreciate here, nuclei were evident within these organisms when viewed through the microscope. **(Right)** This slide demonstrates peripheralization of amastigotes within histiocytes or the marquee sign. Note the nucleus and opposite small kinetoplast in one of the amastigotes.

**Peripheral Localization of Amastigotes Within Histiocytes**



**Numerous Amastigotes With Pink Nuclei on Giemsa Stain**



**(Left)** High-power histologic section from a patient with leishmaniasis shows the small amastigotes located peripherally within histiocytes (the marquee sign) and the small nuclei that are also present. **(Right)** Another Giemsa-stained section demonstrates multiple amastigotes from a biopsy of cutaneous leishmaniasis. Note the very small pink nuclei present. This rules out other commonly confused organisms such as histoplasmosis.



# Larva Migrans and Currens

## KEY FACTS

### TERMINOLOGY

- Larva migrans
  - Pruritic serpiginous erythematous eruptions caused by penetration and migration of hookworm (intestinal nematode) larvae
- Larva currens
  - Pruritic serpiginous erythematous eruptions caused by penetration and migration of *Strongyloides stercoralis* (soil-transmitted helminth) larvae

### ETIOLOGY/PATHOGENESIS

- Larva migrans
  - Most commonly caused by larva of *Ancylostoma braziliense*, hookworm of dogs and cats
  - Less commonly caused by *Necator americanus*
- Larva currens
  - Variant of larva migrans, caused by *S. stercoralis*, soil-transmitted helminth

- Autoinfection by penetration of perianal skin by larvae excreted in feces

### CLINICAL ISSUES

- Larva migrans
  - Direct inoculation of larvae while walking barefoot on beach or sandbox
  - Pruritic serpiginous eruption extends few cm per day
  - Self-limiting course
- Larva currens
  - Autoinfection by penetration of larvae in feces
  - Pruritic serpiginous eruption extends 10 cm per day
  - Chronic course

### MICROSCOPIC

- Small cavities left by parasite in stratum corneum with spongiosis and dermal mixed infiltrate with eosinophils
- Parasite is not commonly seen in epidermis

Larva Migrans

(Left) Larva migrans presents as serpiginous erythematous eruption caused by penetration and migration of hookworm larva. (Courtesy P.M. Southern, Jr., MD.)

(Right) A hookworm (*Ancylostoma braziliense*) larva is seen on this wet mount preparation. (Courtesy Division of Parasitic Diseases and Malaria CDC.)



Hookworm Wet Mount

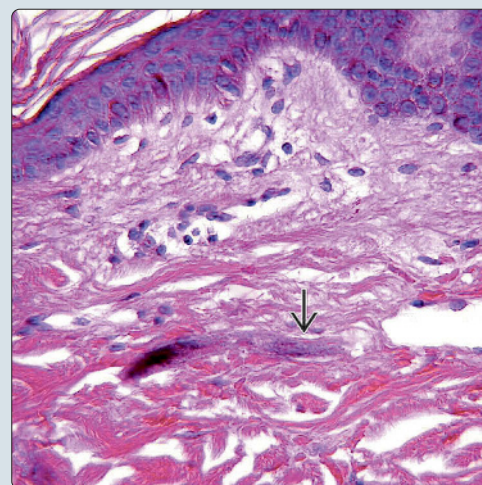


Strongyloides Wet Mount

(Left) *Strongyloides stercoralis* larva on wet mount shows a rhabditoid esophagus and prominent genital primordium. (Courtesy Division of Parasitic Diseases and Malaria CDC.) (Right) *S. stercoralis* larva can sometimes be found in the dermis. Note the absence of inflammation around the larva. (Courtesy M.R. Morrell, MD.)



Larva in Dermis





## TERMINOLOGY

### Synonyms

- Creeping eruption, ground itch, dew itch

### Definitions

- Larva migrans
  - Pruritic serpiginous erythematous eruptions caused by penetration and migration of hookworm (intestinal nematode) larvae
- Larva currens
  - Pruritic serpiginous erythematous eruptions caused by penetration and migration of *Strongyloides stercoralis* (soil-transmitted helminth) larvae

## ETIOLOGY/PATHOGENESIS

### Larva Migrans

- Penetration and migration of hookworm larvae
  - Most commonly caused by larva of *Ancylostoma braziliense*, hookworm of dogs and cats
  - Less commonly caused by *Necator americanus*
  - Other hookworms that may cause this condition include *Ancylostoma caninum*, *Uncinaria stenocephala*, and *Bunostomum phlebotomum*
- Direct inoculation of larvae while walking barefoot on beach or sandbox

### Larva Currens

- Variant of larva migrans, caused by *S. stercoralis*, soil-transmitted helminth
- Autoinfection by penetration of perianal skin by larvae excreted in feces
- Autoinfective life cycle allows larvae to increase in numbers without reinfection from outside
  - Human is principal host of *S. stercoralis*
  - Decades-long persistence of infection

## CLINICAL ISSUES

### Site

- Larva migrans: Mostly feet and occasionally other exposed area
- Larva currens: Skin lesions originate in perianal area

### Presentation

- Larva migrans
  - Erythematous pruritic papule that starts forming tortuous line 4 days after inoculation
  - Lesion extends 1-2 cm per day
  - If not treated, larvae die in 2-8 weeks
  - Loeffler syndrome
    - Rare complication beyond skin
    - Patchy infiltration of lung and peripheral eosinophilia
- Larva currens
  - Serpiginous migrating pruritic eruptions that originate in perianal area
  - Lesion extends 10 cm per day
  - Systemic strongyloidiasis
    - Often chronic disease with systemic symptoms: Abdominal pain, diarrhea, constipation, nausea, vomiting, pneumonitis, urticaria, eosinophilic folliculitis, and peripheral eosinophilia

- Fetal disseminated infections may occur in immunosuppressed patients
  - Fulminant illness with widespread petechiae and purpura (fetal hyperinfection)
  - Periumbilical ecchymoses: Thumbprint sign

### Treatment

- Drugs
  - Ivermectin, albendazole, thiabendazole

### Prognosis

- Larva migrans: Self-limited
- Larva currens: Chronic

## MACROSCOPIC

### General Features

- Serpiginous erythematous linear plaque

## MICROSCOPIC

### Histologic Features

- Small cavities left by parasite located in stratum corneum
- Various spongiosis
- No inflammatory reaction around larva when it can be found (about 0.5 mm thick and up to 10 mm long)
- Mixed infiltrate of lymphocytes, histiocytes, and numerous eosinophils
- Parasite is not commonly seen in epidermis

## ANCILLARY TESTS

### Serologic Testing

- Moderate peripheral blood eosinophilia

### Stool Testing

- Direct microscopic examination for larvae

## DIFFERENTIAL DIAGNOSIS

### Tinea

- Direct microscopic examination of skin scrapings with KOH solution demonstrates hyphae

### Cutaneous Larva Migrans Type Myiasis

- Caused by exposure to infested cattle or infested horses

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Serpiginous migrating eruption
  - Larva migrans: Extends 1-2 cm per day
  - Larva currens: Extends 10 cm per day

### Pathologic Interpretation Pearls

- Small cavities left by parasite located in stratum corneum, but parasite is not commonly seen

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2. Lacarrubba F et al: Dermatoscopy in inflammatory and infectious skin disorders. *G Ital Dermatol Venereol.* 150(5):521-31, 2015
3. Marcos LA et al: Update on strongyloidiasis in the immunocompromised host. *Curr Infect Dis Rep.* 13(1):35-46, 2011

## Onchocerciasis

## KEY FACTS

## TERMINOLOGY

- Also known as river blindness
- Chronic systemic filarial infection most commonly involving skin and eyes

## ETIOLOGY/PATHOGENESIS

- Caused by filarial nematode *Onchocerca volvulus*
- Transmitted to humans via bite of black fly of genus *Simulium* found near free-flowing waterways

## CLINICAL ISSUES

- Early pruritus and urticaria of face and trunk
- Papulovesicles, plaques, nodules, maculopapular rash
- Small, closely packed or large, widely separated lesions occur anywhere and any time after infection

## MICROSCOPIC





- Lymphohistiocytic inflammation with eosinophils and histiocytes surrounding microfilariae in dermis

- Microfilariae can occur in absence of inflammation and may be seen in lymphatic spaces
- Microfilariae vary in length from 220-360  $\mu\text{m}$  and have finely tapered tail
- Onchocercoma: Bundle of adult worms encased by lymphohistiocytic inflammation and fibrosis
- Microfilariae vary in length and width from 220-360  $\mu\text{m}$  and 5-9  $\mu\text{m}$ , respectively

## TOP DIFFERENTIAL DIAGNOSES

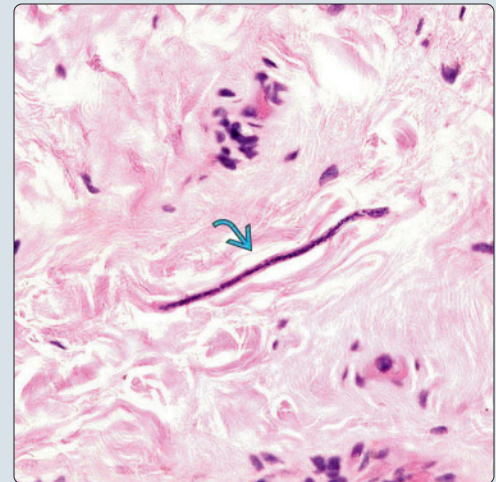
- Cysticercosis (*Taenia solium*)
  - Larval phase of *T. solium* shows characteristic scolex that allows identification
- *Mansonella streptocerca* (Streptocerciasis)
  - Another microfilaria that can be seen in dermis
  - Lacks side-by-side anterior nuclei of onchocerciasis

Hyperpigmented Papules, Lichenified Plaques and Nodules






(Left) Numerous hyperpigmented papules , lichenified plaques , and nodules  are seen here diffusely involving the lower leg of a patient who recently returned from Africa. (Right) Microfilariae  occur in the absence of inflammation and can be seen free within tissue.

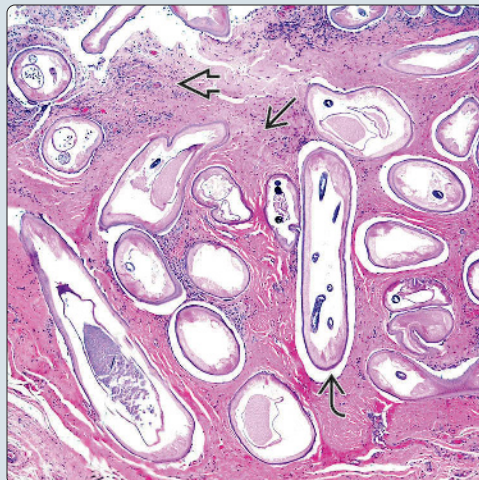


Microfilaria Free in Tissue

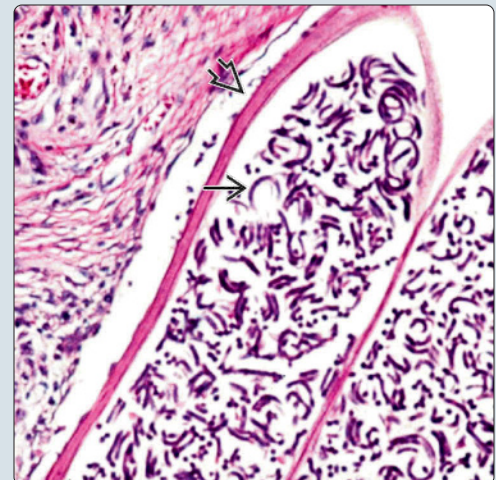


Onchocercoma With Numerous Adult Worms

(Left) Onchocercoma has an outer wall of dense fibrous tissue  that extends in between and encases the coiled filarial adult worms . Chronic lymphohistiocytic inflammation, eosinophils, and granulation tissue are seen . (Right) Numerous small microfilaria  are seen within the lumen of a larger adult gravid female worm .



Microfilariae Within Gravid Female Worm





## TERMINOLOGY

### Synonyms

- River blindness

### Definitions

- Chronic systemic filarial infection most commonly involving skin and eyes

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- Caused by filarial nematode *Onchocerca volvulus*
- Life cycle
  - Transmitted to humans via bite of *Simulium* black fly, found near free-flowing waterways
  - Bite results in microfilariae entering skin and developing into adult worms in subdermal connective tissues

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Most cases occur in endemic areas of Africa, Latin America, and Yemen
  - Imported cases seen in USA
- Age
  - All ages may be infected
  - More severe disease manifestations seen in older patients due to repeated exposures

### Presentation

- Skin
  - Early focal or generalized pruritus and transient urticaria of face and trunk
  - Acute onchocercarial dermatitis with papulovesicles, hyperpigmentation, edema, and erythema
  - Maculopapular rash with small, closely packed or large, widely separated lesions
    - Can appear anywhere on the body and at any time after infection
  - Lichenification, atrophy (lizard skin), and dyspigmentation (leopard skin) are chronic manifestations
  - Bleeding, ulceration, and secondary infection may occur due to scratching
  - Onchocercomas, subcutaneous fibrous nodules filled with bundles of adult worms, occur over bony prominences but can be seen anywhere on body including deep sites (pelvis)
    - No correlation between number of nodules and microfilarial load or disease severity
- Ocular
  - Conjunctivitis, photophobia
  - Involvement of cornea, chorioretinal zone, anterior uveal tract, or optic nerve may occur, ultimately leading to blindness
- Systemic
  - Generalized wasting, arthralgia, fever, femoral/inguinal lymphadenitis

### Laboratory Tests

- Traditional skin snip test, ELISA, PCR, and rapid-format antibody card serologic testing

### Treatment

- Surgical approaches
  - Surgical excision of onchocercoma may help eliminate microfilariae-producing adult worms
- Drugs
  - Antiparasitic agent ivermectin is drug of choice for both prophylaxis and treatment of active disease

### Prognosis

- Ocular disease may lead to blindness after years of recurrent and chronic infection

## MACROSCOPIC

### General Features

- Maculopapular rash, papulovesicles, and subcutaneous fibrous nodules most commonly encountered

## MICROSCOPIC

### Histologic Features

- Early: Mild chronic inflammatory infiltration with lymphocytes, eosinophils, and histiocytes surrounding microfilariae
  - Microfilariae occur in absence of inflammation, and flame figures can be seen with abundant eosinophils
- Chronic: Parakeratosis, hyperkeratosis, epidermal acanthosis, dilated lymphatics, tortuous dermal vessels, pigment incontinence, and dermal fibrosis
- Onchocercoma: Bundles of adult worms encased by lymphohistiocytic inflammation and fibrosis-forming nodule

### Cytologic Features

- Microfilariae vary in length and width from 220-360 µm and 5-9 µm, respectively
- Cephalic space (7-13 µm) followed by close side-by-side first 2 or 3 anterior nuclei, caudal space (9-15 µm) preceded by elongated terminal nuclei, and finely tapered tail

## DIFFERENTIAL DIAGNOSIS

### Cysticercosis (*Taenia solium*)

- Larval phase of *T. solium* shows characteristic scolex that allows identification

### Streptocerciasis (*Mansonella streptocerca*)

- Another microfilaria that can be seen in dermis
- Lacks side-by-side anterior nuclei of onchocerciasis

## SELECTED REFERENCES

1. Lupi O et al: Mucocutaneous manifestations of helminth infections: Nematodes. *J Am Acad Dermatol.* 73(6):929-44, 2015
2. Murdoch ME: Onchodermatitis. *Curr Opin Infect Dis.* 23(2):124-31, 2010
3. Nguyen JC et al: Cutaneous onchocerciasis in an American traveler. *Int J Dermatol.* 44(2):125-8, 2005
4. Elgart ML: Onchocerciasis and dracunculosis. *Dermatol Clin.* 7(2):323-30, 1989

## Schistosomiasis

## KEY FACTS

## TERMINOLOGY

- Schistosomes are trematodes (flukes) or flatworms
  - Schistosoma haematobium*: Infects urinary system
  - Schistosoma japonicum*: Primarily infects liver
  - Schistosoma mansoni*: Infects intestines

## ETIOLOGY/PATHOGENESIS

- Schistosomes &/or their eggs lodge in vessels

## CLINICAL ISSUES

- Sudden widespread eruption of red urticarial pruritic papules on uncovered or exposed skin
- Subsides and recurs for several days
- Some cercariae (*S. japonicum*) that lodge into skin can cause severe urticarial eruption

## MICROSCOPIC


- Epidermal spongiosis and dermal edema

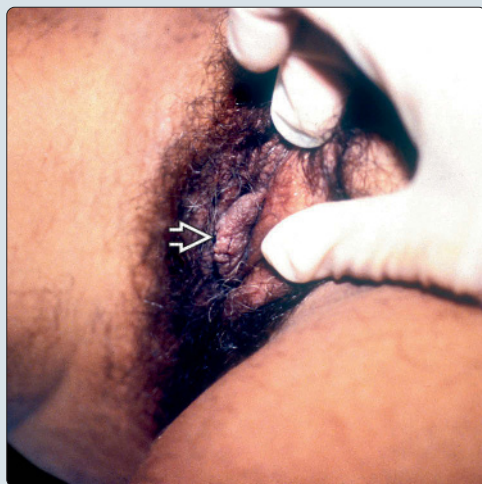
- Mixed inflammatory infiltrate of predominately neutrophils with few eosinophils
- Dermis may contain ova or worms with associated granulomatous reaction
- Eggs with terminal spine = *S. haematobium*; lateral spine = *S. mansoni*; and lateral knob = *S. japonicum*

## TOP DIFFERENTIAL DIAGNOSES

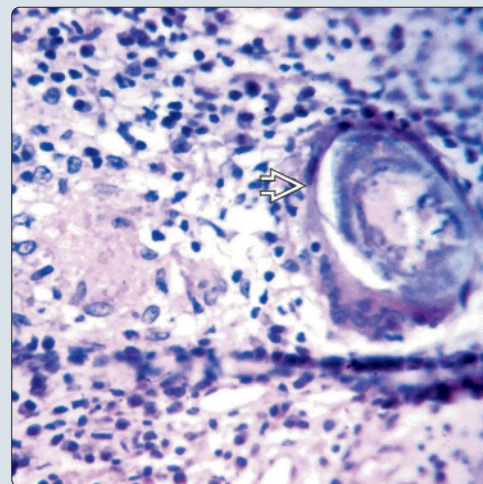
- Seabather's eruption
- Urticaria
- Eczema
- Lichen planus
- Calciophylaxis
- Wells syndrome (eosinophilic cellulitis)

Labia Majora Swelling


(Left) Clinical photograph shows schistosomiasis of the labia majora presenting as swelling  that mimics warts. (Courtesy M. Ramos-e-Silva, MD, PhD.) (Right) Histopathology of schistosomiasis of the vulva demonstrates a single oval egg  amid a chronic inflammatory infiltrate. (Courtesy M. Ramos-e-Silva, MD, PhD.)

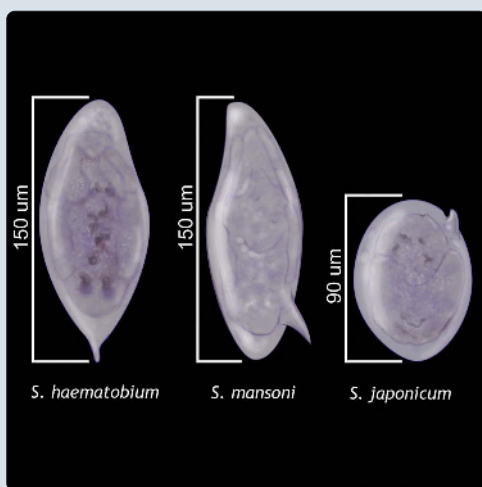


Oval Egg

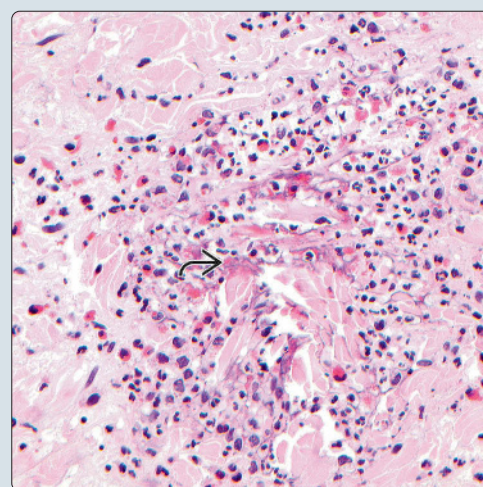


Size and Shape of Schistosome Eggs

(Left) If schistosome eggs can be identified in tissue, their size, shape, and location of the spine (terminal in *Schistosoma haematobium*, lateral in *Schistosoma mansoni*, and no spine or lateral knob in *Schistosoma japonicum*) can help identify the species. (Right) The flame figures found in Wells syndrome  with surrounding eosinophils may mimic dermal schistosomiasis.



Flame Figures in Wells Syndrome





**TERMINOLOGY****Synonyms**

- Bilharziasis, cercarial dermatitis, swimmer's itch (fresh water), clam digger's itch (salt water)

**Definitions**

- Schistosomes are trematodes (flukes) or flatworms
- 3 common species
  - *Schistosoma haematobium*: Infects urinary system
  - *Schistosoma japonicum*: Primarily infects liver
  - *Schistosoma mansoni*: Infects intestines

**ETIOLOGY/PATHOGENESIS****Environmental Exposure**

- Exposure to feces-contaminated water in tropical areas
- Adult worms live in venous system of liver, intestines, or bladder of their definitive hosts (birds, mammals, and humans)
- Eggs are passed through feces and urine into fresh water
  - Eggs hatch; miracidia penetrate body of snail (intermediate host)
- Miracidia develop into swimming cercariae, attach themselves to humans or other animals
- Some species are able to penetrate through skin and enter bloodstream
  - Travel through lungs to gastrointestinal and genitourinary tracts, renewing their lifecycle
- Burrowing produces local inflammatory reaction
  - Rash and pruritus (swimmer's itch)

**CLINICAL ISSUES****Epidemiology**

- Incidence
  - Episodic: Usually occurs during summer months
    - History of exposure to contaminated water
  - More common in China and underdeveloped world countries

**Presentation**

- Sudden widespread eruption of red urticarial pruritic papules on uncovered or exposed skin
  - Subsides and recurs for several days
- Some cercariae (*S. japonicum*) that lodge into skin can cause severe urticarial eruption
  - Fever, malaise, abdominal cramps, arthritis, and lymphadenopathy (Katayama fever)
- In visceral schistosomiasis, pneumonitis, gastrointestinal pain, anemia, eosinophilia, and diarrhea can occur
- Cutaneous granulomas secondary to deposition of eggs in vessels (bilharziomas) occurs in anogenital area
- Genitourinary worms can lodge in bladder and cause bladder cancer

**Treatment**

- Drugs
  - Praziquantel
  - Topical corticosteroids and oral histamines
- Preventative
  - Avoid exposure to contaminated water

- Thoroughly rinse and dry after exposure

**Prognosis**

- Long-term sequelae secondary to chronic inflammation possible in untreated patients
  - Eventual malignancy

**MACROSCOPIC****General Features**

- Swimming cercariae are colorless multicellular organisms about 1 mm long

**MICROSCOPIC****Histologic Features**

- Epidermal spongiosis and dermal edema
- Mixed inflammatory infiltrate of predominately neutrophils with few eosinophils
- Dermis may contain ova or worms with associated granulomatous reaction
- ± necrosis
- ± calcification of eggs

**Cytologic Features**

- Eggs with terminal spine = *S. haematobium*; lateral spine = *S. mansoni*; and lateral knob = *S. japonicum*

**ANCILLARY TESTS****Ova and Parasite Examination**

- Eggs measure < 1 mm, and certain species exhibit spine (terminal, lateral)

**DIFFERENTIAL DIAGNOSIS****Seabather's Eruption**

- No eggs or worms
- Rash under swimwear after swimming in ocean

**Urticaria**

- No eggs or worms
- Diffuse interstitial neutrophils and eosinophils with dermal edema

**Eczema**

- No eggs or worms
- Epidermal spongiosis
- Superficial perivascular lymphocytic infiltrate

**Lichen Planus**

- No eggs or worms
- Lichenoid infiltrate with vacuolar interface change

**Calciphylaxis**

- Metastatic calcification primarily involving vessels of skin

**Wells Syndrome (Eosinophilic Cellulitis)**

- Diffuse dermal eosinophilic infiltration
- Flame figures

**SELECTED REFERENCES**

1. Al-Karawi KS et al: Ectopic cutaneous schistosomiasis. *Int J Dermatol*. 43(7):550-1, 2004

# Dirofilariasis

## KEY FACTS

### TERMINOLOGY

- Rare subcutaneous parasitic infection of nematodes transmitted to humans from infected animals by mosquitoes

### CLINICAL ISSUES

- Majority of reported cases in United States are from Florida
- Most cases in North America caused by *Dirofilaria tenuis*, *Dirofilaria ursi*, or *Dirofilaria subdermata*
- 1 or more firm, erythematous, tender, subcutaneous nodules measuring 1-2 cm in diameter, appearance of which is due primarily to *D. tenuis*, *Dirofilaria repens*, and *D. ursi*
- Location includes areas not covered by clothing, such as head, neck, and extremities
- If not detected, worm will die in nodule, which eventually develops into foreign body granuloma
- Excisional biopsy of skin lesion(s) leads to diagnosis and cure

### MACROSCOPIC

- Subcutaneous skin nodules are usually solitary, erythematous, and tender; pulmonary lesions are usually asymptomatic and coin-shaped on imaging

### MICROSCOPIC

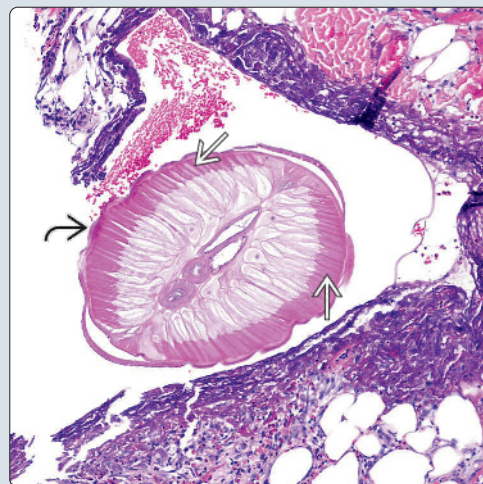
- Parasite appears as tightly convoluted worm with cuticle measuring 125-250  $\mu\text{m}$  in nodule's center
- *D. repens* and *D. tenuis* possess thickened cuticle with longitudinal ridges and transverse striations, whereas *Dirofilaria immitis* possesses smooth cuticle
- Nodule surrounded by inflammatory debris, including eosinophils, lymphocytes, plasma cells, and giant cells
- Surrounding fibrosis correlates with degree of degeneration of parasite

*Dirofilaria repens*, Gross

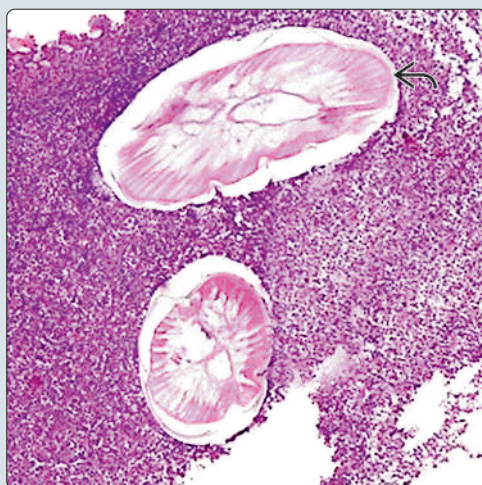


(Left) This example of *Dirofilaria repens* was extracted from a resected subcutaneous palpebral nodule in a patient with dirofilariasis. (Courtesy A. Dzamic, MD.) (Right) Characteristic morphology of *Dirofilaria ursi* is seen in the subcutis of this biopsy specimen from a patient with cutaneous dirofilariasis. Cuticular ridges with multiple layers oblique to the body can be seen.

Cuticular Ridges With Multiple Layers

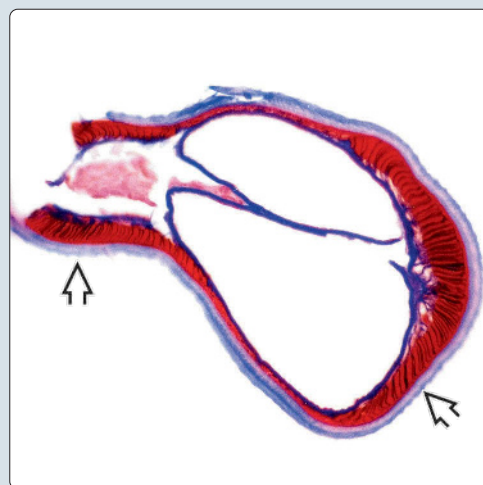


Cuticle and Longitudinal Ridges



(Left) A histologic section of *D. repens* demonstrates 2 organisms with a cuticle and longitudinal ridges surrounded by inflammatory debris. (Right) Transverse section shows *D. repens* with a Masson trichrome stain. Cuticle with longitudinal ridges is visible. (Courtesy A. Dzamic, MD.)

Cuticle With Longitudinal Ridges





## TERMINOLOGY

### Synonyms

- *Dirofilaria* species: *Dirofilaria immitis* (dog heartworms), *Dirofilaria tenuis* (filaria of raccoons), *Dirofilaria repens* (filaria of cats and dogs), *Dirofilaria ursi* (filaria of bears)

### Definitions

- Rare, subcutaneous parasitic infection of nematodes transmitted to humans from infected animals by mosquitoes

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- Caused by filarial nematodes of genus *Dirofilaria*

### Life Cycle

- Definite hosts are dogs, cats, raccoons, and bears
- Transmitted to humans by mosquitoes belonging to genera *Anopheles*, *Aedes*, and *Culex*
- Bite results in transmission of microfilariae to humans, who act as terminal hosts
  - Human-to-human transmission not possible as parasite is unable to reach sexual maturity in human hosts

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Certain species endemic to particular geographic areas
    - Most cases in North America caused by *D. tenuis*, *D. ursi*, or *Dirofilaria subdermata*
    - Most cases in Europe, Africa, and Asia caused by *D. repens*
  - Factors influencing *Dirofilaria* transmission include warm climate, outdoor human activity, lengthy mosquito breeding season, dense mosquito population, and proportion of infected animals
  - Majority of reported cases in United States are from Florida
  - Recent epidemiologic studies indicate increasing prevalence

### Presentation

- Skin
  - 1 or more firm, erythematous, tender, subcutaneous nodules measuring 1-2 cm in diameter, appearance of which are due primarily to *D. tenuis*, *D. repens*, and *D. ursi*
  - Location includes areas not covered by clothing, such as head, neck, and extremities
  - If not detected, worm will die in nodule, which eventually develops into foreign body granuloma
- Pulmonary
  - Result of human infection with *D. immitis* (parasite responsible for heartworms in dogs)
  - Resulting lesion is coin-shaped pulmonary nodule followed by granuloma formation
  - Usually asymptomatic; detected via chest radiograph, computed tomography, or MR
- Ocular
  - Infection of eye and adjacent ocular structures, such as eyelid and orbit, have been reported

- Systemic
  - Possible lymphadenopathy in addition to local inflammatory reaction

### Laboratory Tests

- DNA extraction and PCR; standard antibody tests including ELISA to detect presence of antibodies in serum

### Treatment

- Surgical approaches
  - Surgical removal of lesion is treatment of choice
- Drugs
  - Treatment with antiparasitic medication generally unnecessary
- Preventative measures
  - Prevention of mosquito bites with DEET-based insect repellents, bed nets, and permethrin-treated clothing lowers risk of dirofilariasis transmission

### Prognosis

- Excisional biopsy of skin lesion is curative

## MACROSCOPIC

### General Features

- Subcutaneous nodules are usually solitary, erythematous, and tender; pulmonary lesions are usually asymptomatic and coin-shaped on imaging

## MICROSCOPIC

### Histologic Features

- Parasite appears as tightly convoluted worm with cuticle measuring 125-250  $\mu\text{m}$  in nodule's center
  - *D. repens* and *D. tenuis* possess thickened cuticle with longitudinal ridges and transverse striations, whereas *D. immitis* possesses smooth cuticle
- Nodule surrounded by inflammatory debris, including eosinophils, lymphocytes, plasma cells, and giant cells
- Surrounding fibrosis correlates with degree of degeneration of parasite

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Limited histological differential when nematode is identified with characteristic features, including longitudinal ridges, transverse striations, and cuticle

### Clinical

- Subcutaneous
  - Infections including ascariasis, echinococcosis, hookworms, strongyloidiasis, and tuberculosis
  - Neoplasms of dermal or subcutaneous origin
  - Granulomatous diseases including sarcoidosis and Wegener

## SELECTED REFERENCES

1. Lupi O et al: Mucocutaneous manifestations of helminth infections: Nematodes. *J Am Acad Dermatol*. 73(6):929-44, 2015

# Myiasis

## KEY FACTS

### TERMINOLOGY

- Furuncular myiasis
- Wound myiasis

### ETIOLOGY/PATHOGENESIS

- Caused by infestation by larvae of botfly, blowfly, and screwworm fly
- Most common cause in Americas is *Dermatobia hominis*
- Fly eggs are passively transferred to human host by mosquito vector or on clothing

### CLINICAL ISSUES

- Presents as 2- to 3-cm nodule resembling furuncle
- Usually painful
- Mostly seen on exposed surface, especially head
- Surgical extraction is treatment of choice

### MICROSCOPIC

- Insect has undulating chitinous exoskeleton

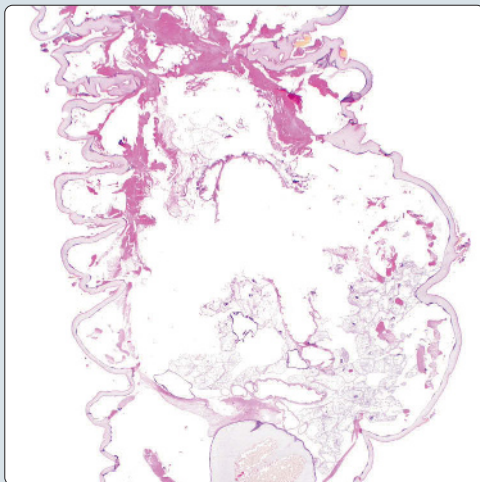
- Pigmented spines (setae) protrude from exoskeleton
- Centrally there are fragments of striated skeletal muscle and intestine

### TOP DIFFERENTIAL DIAGNOSES

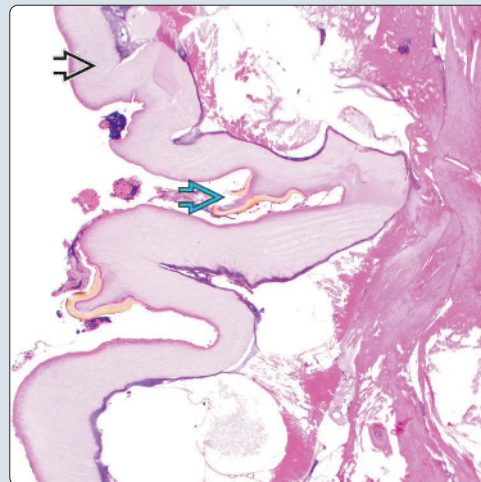
- Tick
  - Only head burrows into skin
  - Lacks pigmented spines
- Tungiasis
  - Burrows on acral skin
  - Exoskeleton lacks pigmented spines
- Scabies
  - Smaller mite which burrows into cornified layer

Scanning Magnification of Botfly

(Left) On scanning magnification, the botfly appears as a large insect with an undulating chitinous exoskeleton. The larva may be embedded with an inflamed cavity in the dermis, or it may be isolated. (Right) The exoskeleton of a botfly is undulating and smooth, formed by chitin. Pigmented spines or spicules (setae) protrude from the exoskeleton and distinguish myiasis.

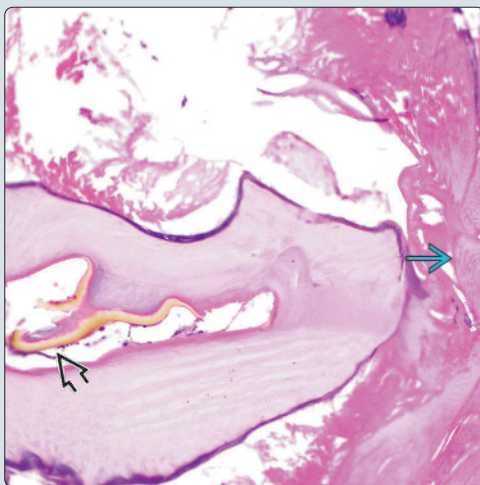


Exoskeleton of Botfly



Pigmented Spines

(Left) The exoskeleton is distinguished by the presence of pigmented spines or setae. Note the striated skeletal muscle on the interior aspect of the larva. (Right) In addition to skeletal muscle, the interior aspect of the larva contains fragments of intestinal epithelium as well as blood contained within luminal spaces.



Intestinal Epithelium





## TERMINOLOGY

### Synonyms

- Furuncular myiasis
- Wound myiasis

### Definitions

- Infestation by larvae (maggots) of Diptera (2-winged flies), which feed on host tissue

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- Fly eggs are transferred to human host by mosquito or fly vector
- Eggs fall off vector and onto host, penetrating skin at site of vector's bite
- Myiasis caused by larvae from several different Diptera flies
  - Botfly: *Dermatobia hominis*
  - Blowfly: *Cordylobia anthropophaga*
  - Screwworm fly: *Cochliomyia hominivorax* and *Chrysomya bezziana*
- Infestation of livestock is more common than infestation of human host

## CLINICAL ISSUES

### Epidemiology

- *D. hominis* found in Central and South America
- *C. anthropophaga* more common in Africa
  - Eggs may be transferred to human host by clothing which has been set out to dry
- Screwworm flies seen in New World and Old World tropical regions

### Presentation

- Slow-growing, tender subcutaneous nodule resembling furuncle
  - Typically measures 2-3 cm in diameter
- May have multiple nodule, but each nodule contains only 1 larva
- May ulcerate, with hemorrhage or purulence
- Typically occurs on exposed skin of face, scalp, and extremities but any site can be affected
  - *Cordylobia* infestation may occur in areas covered by tight-fitting clothes
- Lesions may be painful or pruritic
- Secondary infection by bacteria can occur

### Treatment

- Surgical approaches
  - Surgical extraction of larvae represents definitive treatment
  - May attempt to suffocate maggots by applying petrolatum, glue, oil, or pork fat to wound

### Prognosis

- In untreated lesions, maggot remains in host for 5-10 weeks before emerging to pupate

## MICROSCOPIC

### Histologic Features

- Macroscopic insect may be isolated or seen embedded within ulcer or dermal cavity
- When present, surrounding dermis has variably dense infiltrate of neutrophils, lymphocytes, histiocytes, and eosinophils
- Thick, undulating chitinous cuticle
- Pigmented spines (setae) protrude from exoskeleton
- Contained within exoskeleton are fragments of intestinal epithelium, skeletal muscle, blood

## DIFFERENTIAL DIAGNOSIS

### Tungiasis

- Caused by sand flea *Tunga penetrans*
- Usually located on feet
- Histology shows flea burrowed into acral skin
  - Lacks pigmented setae

### Tick Infestation

- Tick head burrows, but tick body is external to skin
- Lacks pigmented setae

### Scabies

- Smaller, microscopic organism
- Burrows into cornified layer of epidermis
- Dense inflammatory reaction with eosinophils

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Macroscopic insect which burrows into dermis on exposed skin

### Pathologic Interpretation Pearls

- Large, macroscopic insect
- Chitinous exoskeleton
- Pigmented setae distinguish myiasis from other ectoparasites like *T. penetrans* and tick
- Striated muscle, intestinal fragments

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# Tungiasis

## KEY FACTS

### TERMINOLOGY

- Ectoparasitic cutaneous disease caused by female flea *Tunga penetrans* or *Tunga trimamillata*, which causes disease by burrowing into skin of feet, typically periungual in location

### ETIOLOGY/PATHOGENESIS

- Tropical and subtropical regions of world are affected
- Caused by small flea *T. penetrans* or *T. trimamillata*

### CLINICAL ISSUES

- Patients from USA or nonendemic areas typically present with 1-2 isolated lesions and have mild disease
  - History of prior travel to tropics
- Patients from endemic areas can have more severe disease with deep ulcerations and tissue necrosis
- Lesions are usually limited to feet or lower legs
  - High predilection for periungual region of toe
- Extraction is curative

- Prognosis is typically excellent in patients from nonendemic areas
  - In patients from endemic areas, severe disease can have debilitating sequelae

### MICROSCOPIC

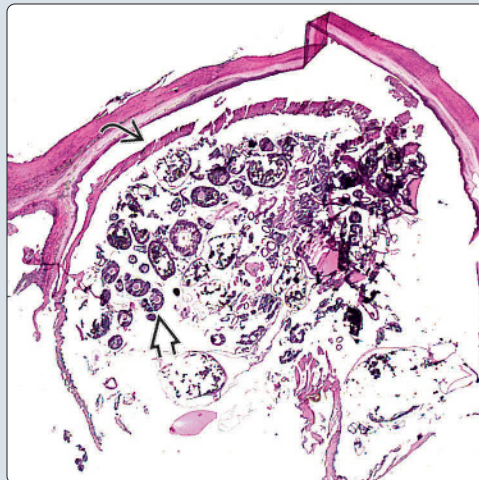
- 3 classic histopathologic features
  - Eosinophilic cuticle
  - Eggs in different stages of development
  - Tracheal rings

### TOP DIFFERENTIAL DIAGNOSES

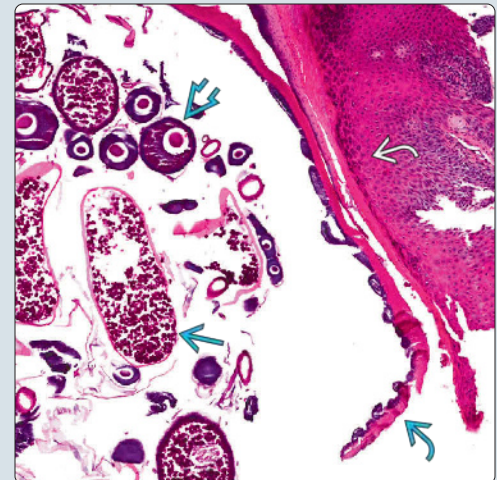
- Myiasis
- Tick
- Scabies
- Onchocerciasis

Subungual Tungiasis With Eosinophilic Cuticle

(Left) Low-power view of tungiasis reveals a large gravid flea in cross section with a surrounding eosinophilic cuticle [A] and eggs at different stages of maturation [B]. (Right) Eosinophilic cuticle [A] is present with blood-filled hollow tubules [B] and eggs [C] at different stages of maturation. Note hypergranulosis [D] and epithelial hyperplasia.

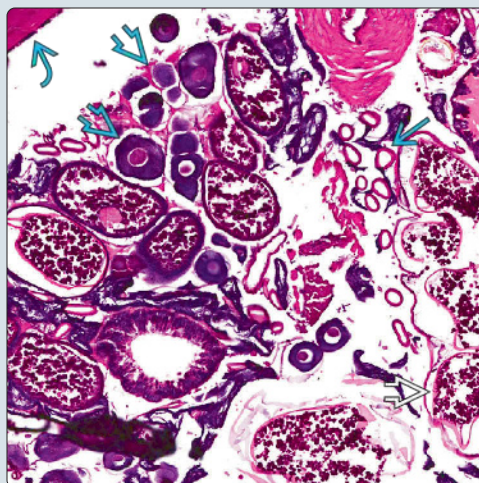


Tungiasis Flea in Cross Section

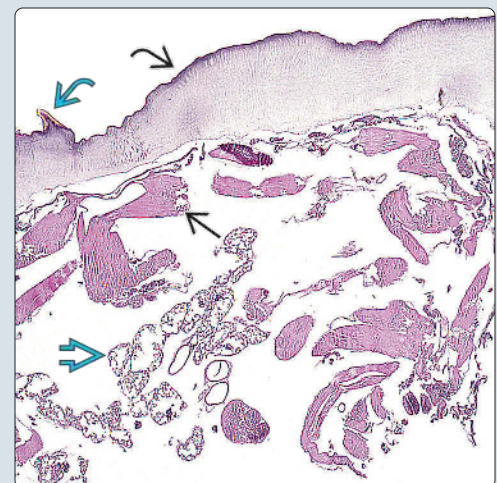


Tracheal Rings and Eggs at Different Stages of Maturation

(Left) High-power view of Tungiasis reveals an eosinophilic cuticle [A], eggs at different stages of maturation [B], and tracheal rings [C]. Note also the hollow tubules [D] (gut) filled with blood. (Right) Although myiasis is usually characteristic clinically, cross-sectional biopsies of the fly larvae can appear similar to tungiasis. Cuticular spines [A], a thick chitinous shell [B] with striated muscle [C] directly beneath and fat bodies [D] help differentiate.



Chitinous Shell, Striated Muscle and Fat Bodies of Myiasis





## TERMINOLOGY

### Definitions

- Ectoparasitic cutaneous disease caused by female flea *Tunga penetrans* or *Tunga trimamillata*, which causes disease by burrowing into skin of feet, typically periungual in location

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- Flea is found in numerous soils, but sandy ground is preferred
- Tropical and subtropical regions of world are affected
  - Includes Mexico, Central and South America, sub-Saharan Africa, and Caribbean

### Infectious Agents

- Caused by small flea *T. penetrans* or *T. trimamillata*
  - Also known as sand flea, chigoe flea, jigger, chica, pico, nigua, chique, puce-chique
- Female fleas burrow into epidermis of host: Humans, dogs, cats, and pigs are most common
  - Numerous other hosts have been reported from cattle to elephants

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - More highly prevalent in impoverished areas

### Presentation

- Patients from USA or nonendemic areas typically present with 1-2 isolated lesions and have mild disease
  - History of prior travel to tropics
- Patients from endemic areas can have more severe disease with deep ulcerations and tissue necrosis
- Lesions are usually limited to feet or lower legs
  - High predilection for periungual region of toe
    - Tip, plantar, or dorsal aspect of toes also commonly affected
  - Heels &/or sole of foot also commonly involved
  - Reason for this clinical predilection is due to fleas limited jumping ability

### Treatment

- Surgical approaches
  - Extraction is curative
    - Should be done under sterile conditions
    - Topical antibiotic should be applied to area after extraction

### Prognosis

- Typically excellent in patients from nonendemic areas
  - Patients often present within 1 week of flea penetration to physician's office
- In patients from endemic areas, severe disease can have debilitating sequelae

## MICROSCOPIC

### Histologic Features

- Burrow seen on acral skin
- 3 classic histopathologic features
  - Eosinophilic cuticle
  - Eggs in different stages of development
  - Tracheal rings
- Other structures that can be seen
  - Intraparasitic red blood cells (blood-filled gut)
  - Oviducts
  - Midgut
  - Hypodermis
  - Hypertrophied striated muscle
  - Bacterial colonies (cocci in chains and clusters)
    - Suggests later clinical stage (involution)
- Host changes include
  - Basal hyperplasia, parakeratosis, hyperkeratosis, acanthosis, hypergranulosis, papillomatosis, and spongiosis
  - Acute and chronic inflammation ± microabscesses may be seen in subjacent dermis
    - Microabscesses typically present in stage 3b
    - Inflammatory cells can include neutrophils, lymphocytes, eosinophils, and histiocytes

## DIFFERENTIAL DIAGNOSIS

### Histopathologic

- Myiasis
  - Larva has thick, undulating chitinous shell with cuticular spines and pigmented setae
    - Striated muscle is found directly under entire cuticle (shell)
  - Fat bodies present
  - Clinically patient reports crawling sensation (movement within lesion)
- Tick
  - Often attached to skin (not burrowed beneath epidermis as in tungiasis)
  - Clinically, much easier to tell apart as ticks attach superficially to skin (with only head being under skin)
- Scabies
  - Mites are much smaller than fleas histologically
  - Mites usually located within stratum corneum (vs. flea being burrowed underneath epidermis)
- Onchocerciasis
  - Microfilariae are often more deep seated (in subcutaneous nodules) and are very small worms embedded in fibrous stroma
  - Adult worms may be found in subcutaneous nodules
    - Histologically adult females are larger, but contain double uterus with microfilariae located within

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1. Feldmeier H et al: Tungiasis—a neglected disease with many challenges for global public health. *PLoS Negl Trop Dis*. 8(10):e3133, 2014
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## Pediculosis

## KEY FACTS

## ETIOLOGY/PATHOGENESIS

- Infestation caused by 3 types of lice: Head louse (*Pediculus humanus capitis*), pubic louse (*Phthirus pubis*), and body louse (*Pediculus humanus corporis*)

## MACROSCOPIC

- Erythematous papules indicative of hypersensitivity reaction at bite sites
- Nits or lice may be visualized associated with hair shafts (head and pubic lice)
- Nits or lice can be found in clothing or bedding of affected individuals (body lice)
- Nits (eggs) appear as small white structures, strongly adherent to hair shaft 0.2-2.0 cm from scalp

## MICROSCOPIC

- Intradermal hemorrhage, wedge-shaped dermal inflammation with eosinophils

- Head and body louse (*P. humanus capitis* and *P. humanus corporis*)
  - 3-4 mm long, 3 pairs of legs, elongate body, and thin head with narrow mouth parts
- Pubic louse (*P. pubis*)
  - 3 mm long, 3 pairs of legs, short, wide body reminiscent of crab, thin head with wide mouth parts
- Nits (all 3 species)
  - 1 mm long, teardrop shaped, translucent with apical operculum (cap)

## TOP DIFFERENTIAL DIAGNOSES

- Non-lice insect bites (different clinical picture)
- Dried hairspray (easy to remove from hair shaft, unlike nits)
- Scabies (similar bite pattern on histology; scabies or burrows may be seen in biopsy)
- Dermatophyte infection (PAS-positive hyphae)
- Delusions of parasitosis (excoriations on histology, no bite pattern on histology)

Excoriations and Visible Louse in Pediculosis Pubis

(Left) Clinical photograph shows pediculosis pubis (pubic lice) that are seen as small dark spots adjacent to hair shafts [A]. The skin also has excoriated crusts [B] from scratching. Pubic lice, similar to head lice (pediculosis capitis), live in human hair. (Right) Clinical photograph shows pediculosis capitis (head lice) with nits that appear as white dots [C] stuck on hair shafts. Both pubic and head lice lay eggs (nits) that are strongly adherent to the hair shaft, just a few millimeters above the skin surface.

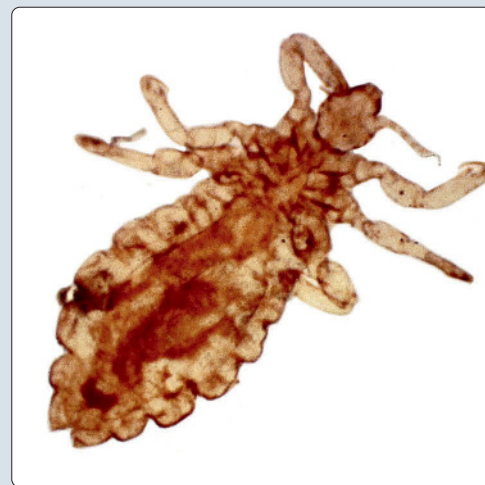


White Nits of Pediculosis Capitis



Pubic Louse Grasping Hair Shaft

(Left) *Phthirus pubis* is shown grasping a hair shaft with claws. Unlike the head louse, which has an elongated body, the pubic lice has a short wide body similar to a crab, hence the colloquial term for pubic lice, "crabs." (Courtesy B. Madke, MD.) (Right) *P. humanus* is an elongated, light-brown, wingless insect. The head and body louse look similar with an ovoid head that is angular and a 9-segmented body. They feed through sucking mouthparts and have claws to help them hold onto the hair shaft.

*Pediculus humanus*



## TERMINOLOGY

### Synonyms

- Human lice, crabs (pubic lice), phthiriasis (public lice infestation)

### Definitions

- Infestation caused by 3 types of lice with specific anatomic body site preference
- Lice or louse: Insect; ectoparasitic organism
- Nit: Egg of lice

## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- 3 types of lice: Head louse (*Pediculus humanus capitis*), pubic louse (*Phthirus pubis*), and body louse (*Pediculus humanus corporis*)
  - Body lice prefer lower temperature, thus live and lay eggs in clothing and bedding
  - Head and pubic lice live in human hair and lay eggs that adhere to hair shafts
  - Small amount of louse saliva is injected into host during feeding, causing mild hypersensitivity reaction and associated pruritus
  - Lice are blood-sucking insects, feeding ~ 5 times/day by biting host

## CLINICAL ISSUES

### Epidemiology

- Transmitted by close physical contact
- Risk factors include young age, crowded environments (schools, day care, multiple family households, etc.), infrequent washing or changing of bedding (for body louse infestations), sexual promiscuity (for pubic louse infestations)
- Head and body louse infestations more common in warm months, pubic louse infestations more common in colder months
- Head louse is more common in school-aged children in urban areas
- Body louse primarily affects homeless

### Presentation

- Pruritus (area involved indicates type of infection)
- Timing of pruritus (body lice feed at night, head/pubic lice feed around clock)
- Nits or lice may be visualized

### Treatment

- Topical and oral treatments have similar efficacies when appropriate retreatment is given for nonresponders
- Lice and nits must be removed from environment to prevent reinfestation
- Effective eradication requires both medication and environmental control

### Prognosis

- Good prognosis with adequate treatment; may need to retreat to ensure eradication of all nits and lice

## MACROSCOPIC

### General Features

- Erythematous papules indicative of hypersensitivity reaction at bite sites
- Excoriations secondary to pruritus and even secondary bacterial or fungal infections of excoriations may occur
- Nits or lice may be visualized associated with hair shafts (head and pubic lice) or clothing (body lice)
- Nits (eggs) appear as small white structures, strongly adherent to hair shaft 0.2-2.0 cm from scalp

## MICROSCOPIC

### Histologic Features

- Intradermal hemorrhage, wedge-shaped dermal inflammation with eosinophils
- Head and body louse (*P. humanus capitis* and *P. humanus corporis*)
  - 3-4 mm long, 3 pairs of legs, elongate body, and thin head with narrow mouth parts
- Pubic louse (*P. pubis*)
  - 3 mm long, 3 pairs of legs, short, wide body reminiscent of crab, thin head with wide mouth parts
- Nits (all 3 species)
  - 1 mm long, teardrop shaped, translucent with apical operculum (cap)

## DIFFERENTIAL DIAGNOSIS

### Non-Louse Insect Bites

- Will have different clinical course and manifestations

### Dried Hairspray

- Easily removed from hair shaft, unlike nits

### Scabies

- Similar bite reactions; lacks nits and has scabetic burrows &/or presence of scabies in biopsy specimen

### Dermatophyte Infection

- Hyphae can be visualized with PAS-F special stain

### Delusions of Parasitosis

- No histologic findings of bite reaction, excoriation, and artifactual lesions

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Identification of lice is necessary for diagnosis
- Presence of nits within 4 cm of scalp is strongly suggestive of infestation

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## KEY FACTS

## ETIOLOGY/PATHOGENESIS

- Mosquito-borne disease
- *Brugia malayi*
- *Brugia timori*
- *Wuchereria bancrofti*

## CLINICAL ISSUES

- 120 million infected worldwide
- 1st acquired in childhood, parasite burden increases over time spent in endemic areas
- Rarely seen in travelers spending short periods of time in endemic regions

## MICROSCOPIC

- Intact male and female adult filariae can be seen in lymphatics
- Granulomatous reaction around dead and dying filariae
- Polypoid endolymphangitis

- Acute lymphangitis and chronic lymphatic dilatation and fibrosis
- Eosinophilic lymphadenitis (Meyers-Kouwenaar syndrome)
- Blood smear light microscopy can be used to differentiate species

## ANCILLARY TESTS

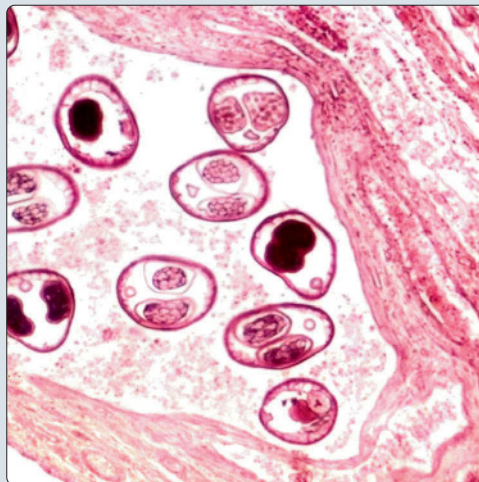
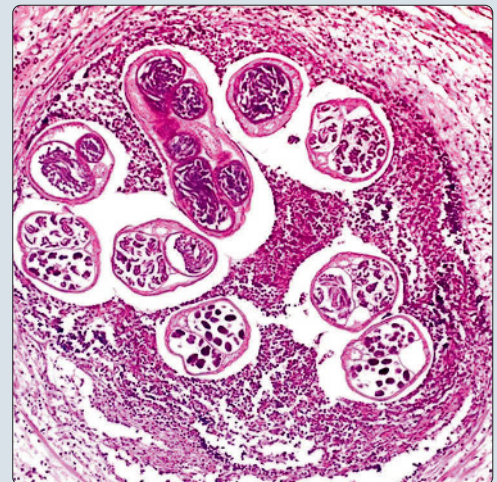
- Antigen detection
  - Circulating filarial antigen can be detected using monoclonal antibodies raised against related species of nematodes

## TOP DIFFERENTIAL DIAGNOSES

- Bacterial or fungal lymphadenitis
- Hydrocele
- Nonfilarial elephantiasis (podoconiosis)
- Nonfilarial lymphedema (Milroy disease)
- Onchocerciasis (*Mansonella streptocerca*)

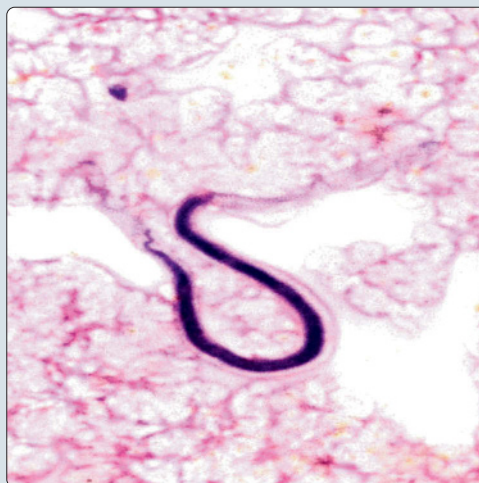
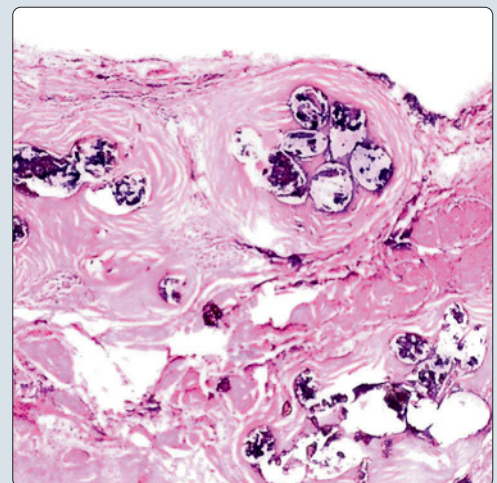
Male *Wuchereria bancrofti* in Cross Section

(Left) Cross sections of dilated spermatic cord lymph vessels demonstrate male *W. bancrofti*; note the lack of microfilaria. (Courtesy Franz von Lichtenberg Collection of Infectious Disease Pathology, BWH.) (Right) Cross sections of female *W. bancrofti* are seen in the epididymis with inflammation. Note the abundant microfilaria. (Courtesy Franz von Lichtenberg Collection of Infectious Disease Pathology, BWH.)

Female *W. bancrofti* With Microfilaria

Sheathed Microfilaria

(Left) A sheathed microfilaria is seen in a Giemsa-stained smear. (Courtesy Franz von Lichtenberg Collection of Infectious Disease Pathology, BWH.) (Right) Pelvic lymphatics contain calcified *W. bancrofti*, as shown here. (Courtesy Franz von Lichtenberg Collection of Infectious Disease Pathology, BWH.)

Calcified Lymphatics With *W. bancrofti*



**TERMINOLOGY****Synonyms**

- Elephantiasis

**Definitions**

- Latin: "Filum" (thread)
- Wuchereria from Otto Wucherer (German physician)
- Brugia from S. L. Brug (Dutch parasitologist)
- Mansonella from Sir Patrick Manson (English tropical medicine expert)

**ETIOLOGY/PATHOGENESIS****Infectious Agents**

- Infectious disease caused by thread-like roundworms of Filarioidea type
- *Wuchereria bancrofti*
  - Filarial nematode transmitted by bites of infected mosquitos
  - Most widely distributed accounting for > 90% of cases
    - Sub-Saharan Africa
    - Southeast Asia
    - India
    - Pacific Islands
    - South America
    - Caribbean
- *Brugia malayi*
  - Filarial nematode transmitted by bites of infected mosquitos
  - China
  - India
  - Southeast Asia
- *Brugia timori*
  - Filarial nematode transmitted by bite of infected mosquitos
  - Timor
- *Mansonella streptocerca*
  - Filarial nematode transmitted by bites of infected midge flies
  - Causes skin nodules in African rain forests (similar to onchocerciasis)
- *Mansonella perstans* and *Mansonella ozzardi*
  - Filarial nematode transmitted by bites of infected midge flies
  - *M. perstans* is found in Sub-Saharan Africa and parts of Central and South America
  - *M. ozzardi* is found in Central and South America

**Vector**

- Mosquito-borne disease (*Wuchereria* and *Brugia*)
  - Vector species vary geographically
    - In Africa, most common vector is *Anopheles*
    - In Americas, most common vector is *Culex*
    - In Pacific and Asia, *Aedes* and *Mansonia* are most common
  - *W. bancrofti* most commonly spread by *Culex*, *Anopheles*, and *Aedes* species
- Midge-borne disease (*Mansonella* species)
  - *Culicoides* species (midge flies)

- *M. ozzardi* is also transmitted by black flies (South America)

**CLINICAL ISSUES****Epidemiology**

- *Wuchereria* and *Brugia* species
  - 120 million infected worldwide
    - Mainly in tropics and subtropics
    - 15 million of those infected have lymphedema of lower limbs
    - 25 million men have genital disease
    - 2/3 of those infected are in Asia
  - 1st acquired in childhood, parasite burden increases over time spent in endemic areas
  - Mosquito not very effective at transmission; therefore, rarely seen in travelers spending short amounts of time in endemic regions
  - Leading cause of disfiguring morbidity worldwide
- *Mansonella* species
  - > 100 million infected worldwide with gross underestimation due to asymptomatic/mild disease

**Presentation**

- *Wuchereria* and *Brugia*
  - Majority are asymptomatic but may have subclinical lymphatic and renal disease
  - Acute phase
    - Fever
    - Lymphadenopathy (genital and axillary)
    - Orchitis/epididymitis
    - Lymphedema of limbs &/or genitals
  - Chronic phase
    - Irreversible lymphedema
  - Florid eosinophilia found in peripheral blood counts
  - Can present as tropical pulmonary eosinophilia secondary to inflammatory response to infection
- *Mansonella* species
  - Majority are asymptomatic
  - *M. perstans*/*M. ozzardi* cause body cavity filariasis
    - Calabar-like swellings, eosinophilia, abdominal pain, fever, headache, pruritus
  - *M. streptocerca* causes cutaneous nodules

**Laboratory Tests**

- Peripheral blood smear
  - Identified *Wuchereria* and *Brugia* species in peripheral blood by microfilarial features
  - Eosinophilia may be present
- Body fluid examination (pleural fluid)
  - Identified *M. perstans* or *M. ozzardi* species by microfilarial features

**Treatment**

- Diethylcarbamazine
  - Contraindicated in patients with concomitant loiasis
- Albendazole
- Ivermectin
- Doxycycline
- Surgical excision of hydroceles may be option in some cases

**Prognosis**

- Chronic lymphedema is irreversible
- Good prognosis if recognized and treated early

**Complications**

- Secondary bacterial infection can be common complication and care should be taken to hygienically maintain affected areas

**IMAGING****Ultrasonographic Findings**

- Testicular ultrasound may show movement of echogenic particles, classically termed "filarial dance"
  - In patients with travel to endemic areas, may be suggestive of filarial infection due to obstruction
  - In patients with no exposure, may represent obstruction for other reasons (post vasectomy)

**MICROBIOLOGY****Parasite Features**

- Humans are only vertebrate host of *W. bancrofti*
- *B. malayi* can infect monkeys and felines, but humans are most common vertebrate host
- *M. perstans* has only human reservoir, while *M. streptocerca* has animal reservoirs
- Life cycle has 5 larval stages in vertebrate host and arthropod vector
  - 3rd stage is transmitted to vertebrate host from mosquitoes/midges
    - Larvae enter circulation via bite wound and migrate to host lymphatics
- Over 6-12 months, mature worms develop (females: 8-10 cm; males: 1/3 that size)
- Adults can survive in human host for 5 years
- Display nocturnal periodicity with peak presence in bloodstream between 10 p.m. and 2 a.m.

**Culture**

- There is no role for culture in diagnosis of filarial worms

**Endosymbiosis**

- Filaria nematodes have endosymbiotic relationship with *Wolbachia* species bacteria
- Death of *Wolbachia* bacteria leads to infertility in nematode

**MICROSCOPIC****Histologic Features**

- Intact male and female adult filariae can be seen in lymphatics, skin nodules, or pleural fluid
- Granulomatous reaction around dead and dying filariae
- Calcified and lamellated granulomatous reaction
- Acute lymphangitis and chronic lymphatic dilatation and fibrosis
- Polypoid endolymphangitis
- Eosinophilic lymphadenitis (Meyers-Kouwenaar syndrome)

**Cytologic Features**

- Microfilaria may appear as coiled structures ± sheath, visible nuclei, and caudal space

- Fragments of adult worms may be present depending on type of sampling

**Differentiation of Filarial Parasites**

- Blood/fluid smear light microscopy can be used to differentiate species
- Filaria are visible on Giemsa stain
- *W. bancrofti* does not have nuclei in its tail and is sheathed
- *B. malayi* has terminal and subterminal nuclei in its tail and is sheathed
- *Mansonella* species are unsheathed
  - *M. perstans* has paired nuclei down to end of tail
  - *M. ozzardi* has single row of nuclei that end before tail
  - *M. streptocerca* has single row of nuclei that extend to end of tail

**ANCILLARY TESTS****Antigen Detection**

- Circulating filarial antigen can be detected using monoclonal antibodies raised against related species of nematodes

**PCR**

- Large-scale prevalence studies are carried out using PCR

**DIFFERENTIAL DIAGNOSIS****Bacterial or Fungal Lymphadenitis**

- Presence of bacteria on Gram or silver stain; presence of fungal forms on silver stain

**Hydrocele**

- Diagnosed with transillumination
- Microscopically seen as loose connective tissue with mesothelial lining
- Chronic hydrocele may have inflammation and fibrosis

**Nonfilarial Elephantiasis (Podoconiosis)**

- Ascending and asymmetric
- Can begin as foot pain, plantar edema, and rigidity of toes
- Rarely involves groin
- Not caused by filarial reaction; rather, caused by reaction to mineral components in volcanic clay

**Nonfilarial Lymphedema (Milroy Disease)**

- Edema with dilated lymphatic spaces
- Lower limb edema present at birth or develops in early infancy

**Onchocerciasis**

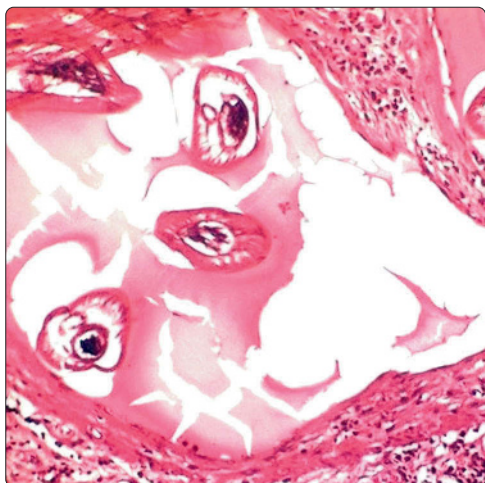
- *Onchocerca* microfilaria have single row of nuclei that do not extend to end of tail or head

**SELECTED REFERENCES**

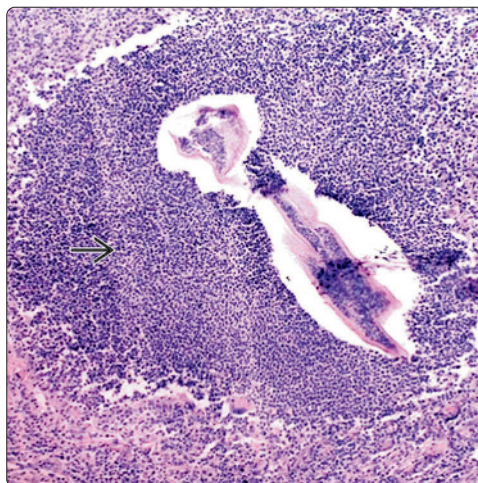
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***W. bancrofti* High Power**

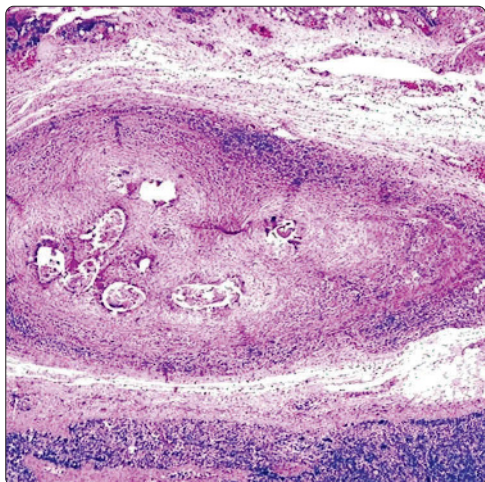


**Filaria Occluding Lymphatics**

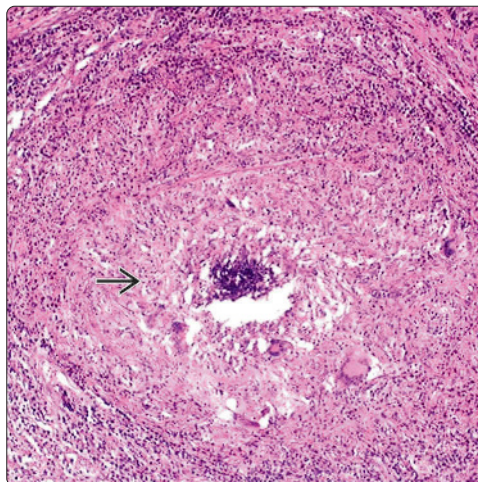



(Left) Cross sections of male *W. bancrofti* are seen in dilated spermatic cord lymph vessels. (Courtesy Franz von Lichtenberg Collection of Infectious Disease Pathology, BWH.) (Right) The filaria become lodged in lymphatics due to intense inflammation  occluding the lymphatic lumina. (Courtesy Franz von Lichtenberg Collection of Infectious Disease Pathology, BWH.)

**Filariae With Granulomatous Inflammation**

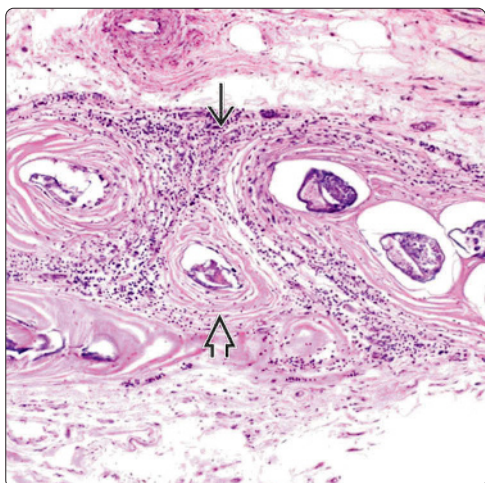


**Granulomatous Inflammation Surrounding Filarial Remnant**

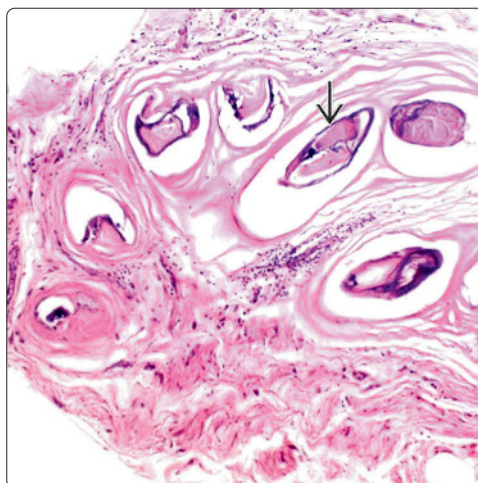





(Left) Degenerating *W. bancrofti* are present in an inguinal lymph node hilus, surrounded by a large granuloma. (Courtesy Franz von Lichtenberg Collection of Infectious Disease Pathology, BWH.) (Right) A granuloma  is present in the spermatic cord, which contains a necrotic filarial remnant. The differential diagnosis would also include tuberculosis. (Courtesy Franz von Lichtenberg Collection of Infectious Disease Pathology, BWH.)

**Lymphatic Wall Thickening in Filariasis**



**Calcified Filariae in Tissue**



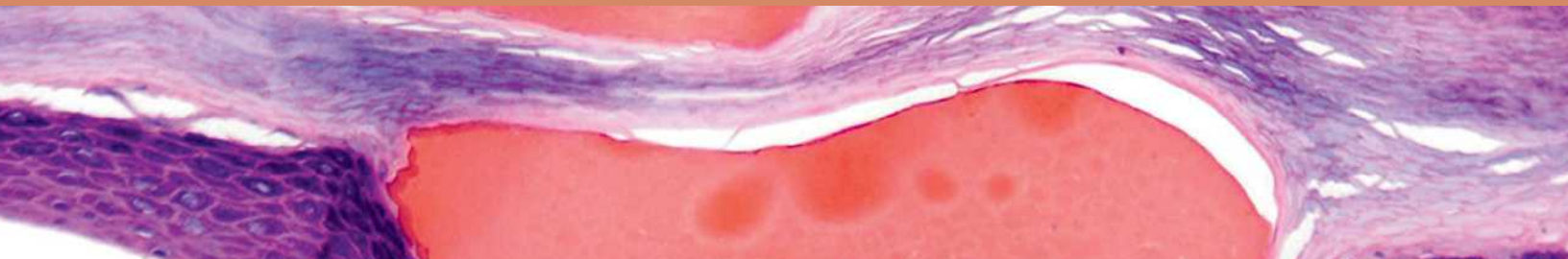
(Left) Inflamed pelvic lymphatics contain *W. bancrofti*. Note the rim of inflammatory cells  and reactive thickening of lymphatic walls . (Courtesy Franz von Lichtenberg Collection of Infectious Disease Pathology, BWH.) (Right) Pelvic lymphatics contain calcified *W. bancrofti*. Note the paired uteri remnants . (Courtesy Franz von Lichtenberg Collection of Infectious Disease Pathology, BWH.)

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SECTION 24

Other



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## KEY FACTS

### TERMINOLOGY

- Endometriosis that occurs in cutaneous tissue often in relation to scar tissue from prior surgery or spontaneously (unrelated to prior scar or surgery)

### CLINICAL ISSUES

- Occurs most commonly near or around umbilicus (villar nodule)
- Most cases (> 70%) occur over scars

### MICROSCOPIC

- Classic findings are endometrial glands surrounded by endometrial stroma ± hemorrhage/hemosiderin deposition

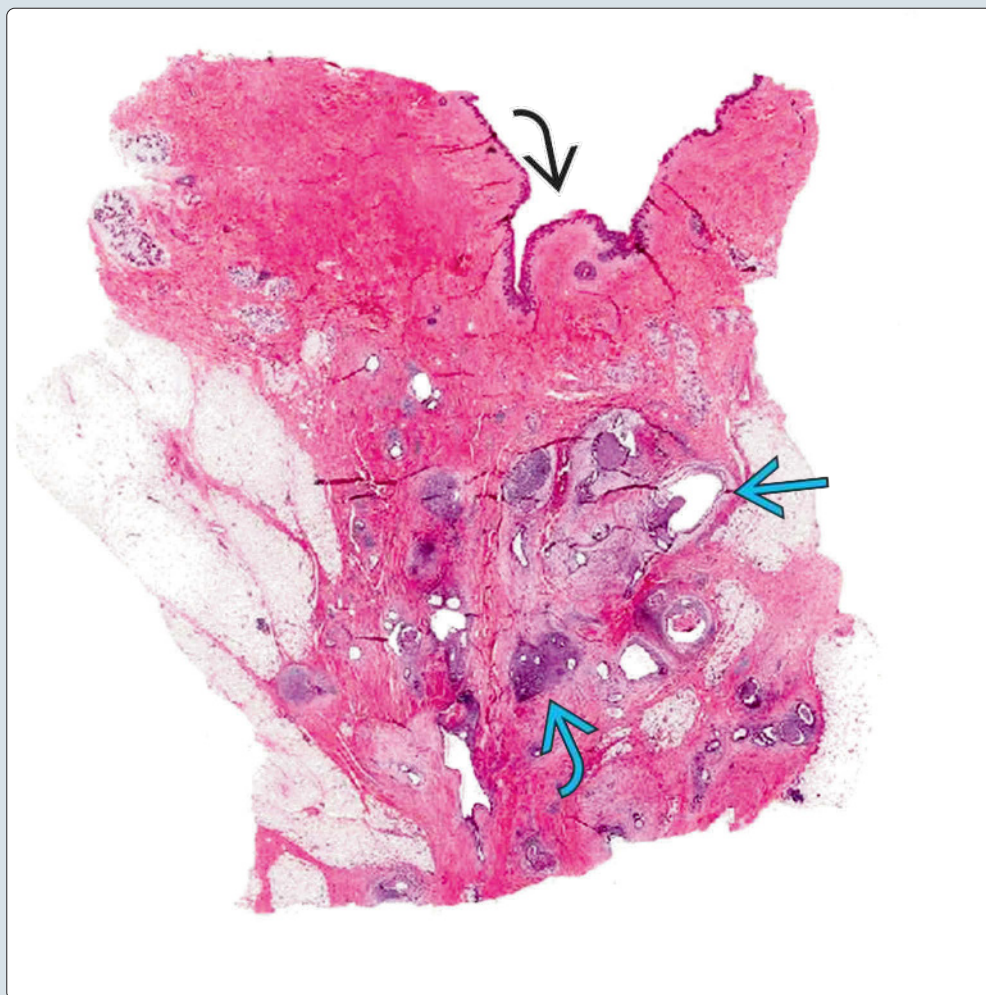
### ANCILLARY TESTS

- CD10 can be used to highlight surrounding endometrial stroma (cytoplasmic staining)
- CK7 and PR should be positive in endometrial glands in almost all cases

### TOP DIFFERENTIAL DIAGNOSES

- Histopathologic
  - Primary or metastatic adenocarcinoma
    - Cells will have more cytologic atypia that is uniform and often conspicuous mitotic figures
    - Endometrial stroma is absent
  - Cutaneous endosalpingiosis
    - Glandular epithelium is ciliated
  - Omphalomesenteric duct cyst/remnant
    - Sharp transition from cutaneous epithelium to enteric mucosa
  - Pyogenic granuloma
    - Nodular or lobular proliferation of small capillaries with surrounding inflammation and edema
  - Hidradenoma papilliferum
    - Papillary fronds as well as cystic, glandular spaces set in collagenous stroma

Umbilical Cutaneous Endometriosis



From low power, note the variably sized glands [blue arrow] with surrounding, associated dense endometrial stroma [black arrow]. Also note the umbilicus in this biopsy specimen [red arrow].



## TERMINOLOGY

### Abbreviations

- Cutaneous endometriosis (CEM)

### Synonyms

- Villar nodule (when occurring near umbilicus)
- Scar endometriosis
- Scar endometrioma

### Definitions

- Endometriosis that occurs in cutaneous tissue, often in relation to scar tissue from prior surgery or spontaneously (unrelated to prior scar)

## ETIOLOGY/PATHOGENESIS

### Can Occur in 2 Circumstances

- Scar-related or secondary to abdominopelvic surgery such as
  - C-sections, laparoscopy/laparotomy, hysterectomy, appendectomy, others
  - Most common type of CEM by far
  - Thought to be secondary to implantation of endometrial tissue in skin during procedure
  - Accounts for > 70% of cases
- Spontaneously
  - Much rarer, accounts for < 30% of cases
  - Etiology unclear
    - One theory proposes transplantation via
      - Retrograde menses
      - Mechanical transplantation
      - Or through hematogenous or lymphatic spread
    - Other theory is in situ presence of endometrial cells via embryonic remnants

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - CEM accounts for < 5% of all cases of endometriosis
  - Approximate total incidence of 0.11%
    - Incidence of ~ 0.30% after C-section
- Age
  - Mean: 34 years
- Sex
  - Exclusively females
    - Endometriosis may occur in some men after long-term hormonal therapy after prostate cancer
    - CEM has not been reported in men to date

### Site

- Occurs most commonly near or around umbilicus (villar nodule)
  - In addition to umbilicus, can also occur on or around perineum, inguinal area, and vulva
- Most cases (> 70%) occur over scars
- ~ 25% of patients with CEM also have pelvic endometriosis

### Presentation

- Usually single, firm or rubbery nodule 1-2 mm to up to 9 cm in size; can be red to blue to brown/black or even flesh-colored
  - Color depends on amount of hemorrhage and depth of ectopic endometrial tissue
  - Mean size is ~ 2 cm
  - Occasionally multiple nodules may be present
- Tenderness, bleeding, pain, swelling, &/or changes in size may occur in sequence with menstrual cycle
  - Some patients may be asymptomatic

### Natural History

- Symptoms typically follow menstrual cycle
  - Lesions may increase in size with increased symptoms (e.g., pain, bleeding, swelling) during menstruation

### Treatment

- Drugs
  - Oral contraceptives, gonadotropin-releasing hormone agonists, and danazol
    - Can help reduce tumor size &/or provide symptomatic relief
    - Only partially effective (surgery is necessary for cure)
- Surgery is mainstay
  - Typically best at end of menses (lesions are smaller)
  - Recurrence is uncommon when surgical margins are clear
  - For larger lesions, synthetic mesh or tissue transfer may be needed for closure

### Prognosis

- Good
  - Recurrence is quite rare (few case reports) with adequate surgical therapy
- Malignant transformation extremely rare (< 1%)
  - Carcinomas such as endometrioid (most common), clear cell, and serous as well as adenocarcinomas have all been reported

## MICROSCOPIC

### Histologic Features

- Classic diagnostic triad includes
  - 1: Endometrial glands
    - Typically mixture of large and small glands
    - Glandular morphology may proliferative, secretory, or menstrual (just as in regular endometrial biopsies)
      - Patients can show mixture of endometrial phases within same lesion
  - 2: Endometrial stroma
    - Spindled cells with basophilic cytoplasm and prominent vascular network
  - 3: ± hemosiderin deposition
    - Free hemosiderin, hemosiderin-laden macrophages, &/or extravasated red blood cells are often seen
      - But not invariably present in all cases
- Must scrutinize for malignant transformation, which, although extremely rare (0.6-0.7% incidence), has been reported

**Cytologic Features**

- Cytology of glandular cells typically ranges from bland to slightly atypical

**ANCILLARY TESTS****Immunohistochemistry**

- CD10 can be used to highlight surrounding endometrial stroma (cytoplasmic staining)
  - Can be helpful in differentiating from stromal reaction that can sometimes surround adenocarcinomas
  - ER and PR immunostains often also highlight stromal cells
- p63 is negative in endometrial glands (vs. endometriosis at other sites)
- CK7 and PR should be positive in endometrial glands in almost all cases
  - ER should also be positive in most cases
    - ER and PR can be lost in decidualized endometriosis, but CD10 will still stain stroma in these cases

**DIFFERENTIAL DIAGNOSIS****Histopathologic**

- Primary or metastatic adenocarcinoma
  - Most important histopathologic differential diagnosis
  - Cells will have more cytologic atypia that is uniform and often conspicuous mitotic figures
  - Endometrial stroma is absent
    - In difficult cases, CD10 can be used to differentiate between stromal response, coexisting sarcoma (extremely rare) and endometrial stroma
    - Exception would be malignant transformation within CEM (extremely rare)
- Cutaneous endosalpingiosis
  - Extremely rare (rarer than CEM)
  - Also has glands with surrounding fibrous stroma, but glandular epithelium is prominently ciliated (vs. CEM)
    - CEM can have rare ciliated cells, but should not be prominent finding
    - Ciliated glandular cells indicate fallopian tube epithelium
  - Stroma is fibrous (vs. endometrial stroma of CEM)
  - No hemosiderin deposition
- Omphalomesenteric duct cyst/remnant
  - Lacks endometrial stroma
  - Sharp transition from cutaneous epithelium to enteric mucosa
    - Enteric mucosa is usually small intestine but may also be gastric
    - Mucosa may sometimes form tubular or cystic structure within dermis
      - Occurs when duct is still patent (very rare)
  - If enteric mucosa is small intestine should stain with CK20 or CDX-2 (both negative in endometrial glands)
  - Clinically presents as umbilical polyp
- Pyogenic granuloma
  - Often ulcerated
  - Often has epithelial collarette (acanthotic downgrowth flanking dermal proliferation)

- Nodular or lobular proliferation of small capillaries with surrounding inflammation and edema
  - Capillaries can be highlighted with vascular markers (CD31, CD34, ERG)
- Hidradenoma papilliferum
  - No endometrial stroma but does have hyalinized stroma, which is CD10(-)
  - Papillary fronds as well as cystic, glandular spaces set in collagenous stroma
    - Decapitation secretion (apocrine differentiation) should be discernible
  - Almost exclusively perianal or vulvar in location
  - Occurs almost exclusively in women (similar to endometriosis)
  - Clinically usually doesn't bleed

**Clinical**

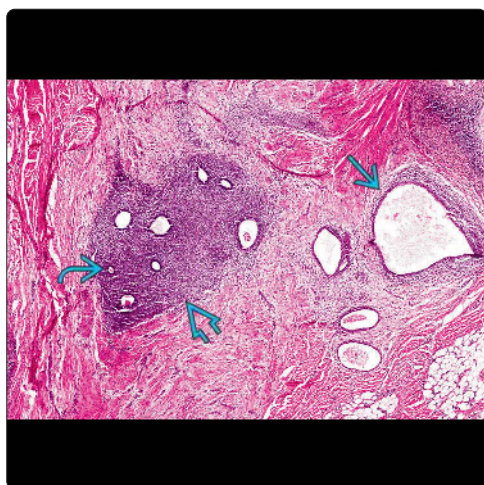
- Sister Mary Joseph nodule (or sign)
  - Is result of metastatic disease and also occurs around umbilicus
  - Most important clinical differential diagnosis
  - Typically older patients
  - Imaging may be helpful in identifying primary tumor
- Hemangioma
  - Bright red, well-demarcated, usually dome-shaped, but smooth surface
  - No fluctuation or changes in relation to menses
- Pyogenic granuloma
  - Constantly bleeding clinically
    - No association with menstrual cycle
  - Bright red, usually crusted and eroded
  - Usually history of trauma at site clinically
  - Typically not painful
- Keloid
  - Skin is usually taught over surface
  - Key is underlying tissue is indurated clinically
  - Can be red early, then usually turns white later
  - Can also be painful
- Melanocytic nevus
  - Covered with smooth, intact skin
  - Usually flesh-colored or varying shades of evenly covered brown and black
  - Does not bleed clinically
  - No association with menses or prior surgery
- Melanoma
  - Poorly demarcated
  - Multiple shades of black, brown, pink, or skin color all in same tumor
  - Does not bleed easily
  - No association with menses

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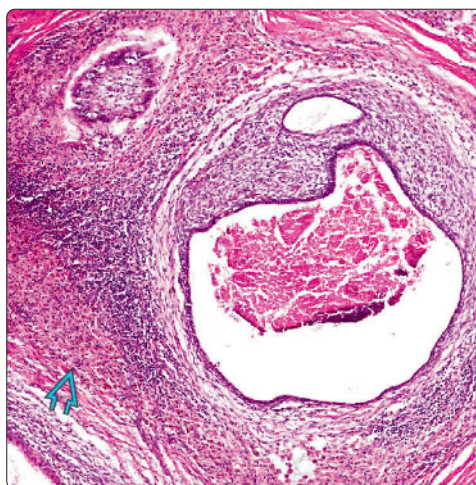
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Mixture of Small and Large Glands

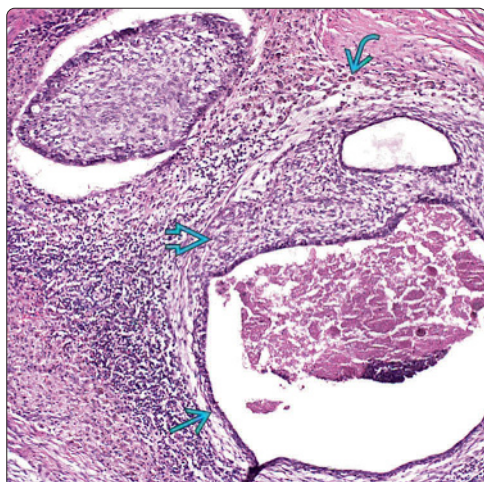


Large Endometrial Gland and Endometrial Stroma

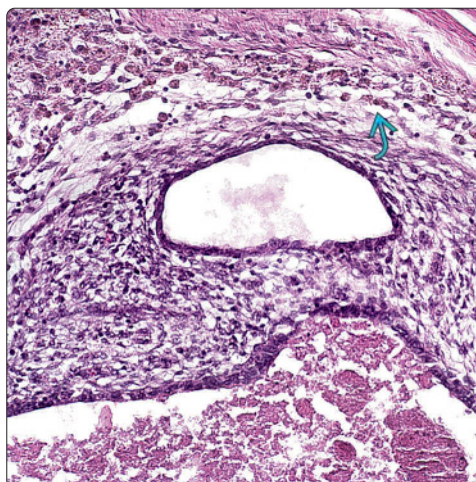






(Left) In cutaneous endometriosis, there is typically a mixture of small  and large  glands intimately associated with dense surrounding endometrial stroma . (Right) A large endometrial gland is pictured here, filled with erythrocytes and containing surrounding endometrial stroma. Note hemosiderin deposition  to the left.

Endometrial Glands, Stroma, and Hemosiderin Deposition

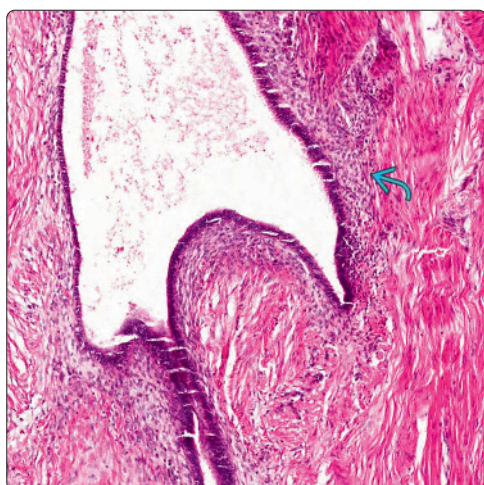


Hemosiderin-Laden Macrophages

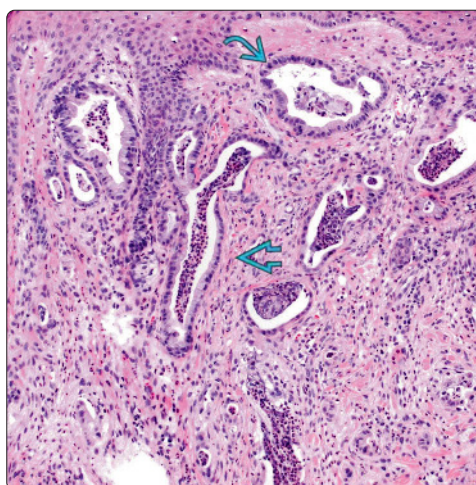





(Left) This high-power view demonstrates the 3 classic feature of cutaneous endometriosis: Endometrial glands , endometrial stroma , and hemosiderin deposition  (hemosiderin-laden macrophages). (Right) High-power view of cutaneous endometriosis demonstrates numerous hemosiderin-laden macrophages  surrounding endometrial glands with associated stroma.

Endometrial Gland and Endometrial Stroma Tangentially Sectioned



Metastatic Adenocarcinoma



(Left) In this section, this endometrial gland is cut in tangentially, so it appears that this gland is infiltrative, but the cytology of the glandular cells are uniform and there is still associated endometrial stroma . (Right) This is an example of a rare metastatic small intestinal (duodenal primary) carcinoma to the skin. Note the hyperchromasia and atypia of the glandular cells  and surrounding desmoplastic stroma . (From DP: Neoplastic Derm, 2e.)



## KEY FACTS

### TERMINOLOGY

- Eosinophilic cellulitis

### CLINICAL ISSUES

- Painful or pruritic edematous plaques or nodules
- May take on variety of morphologies also including urticarial, annular, or bullous
- Often symmetrical
- Lack of warmth, symmetry, and occasional violaceous border suggest diagnosis
- Peripheral blood eosinophilia is common

### MICROSCOPIC

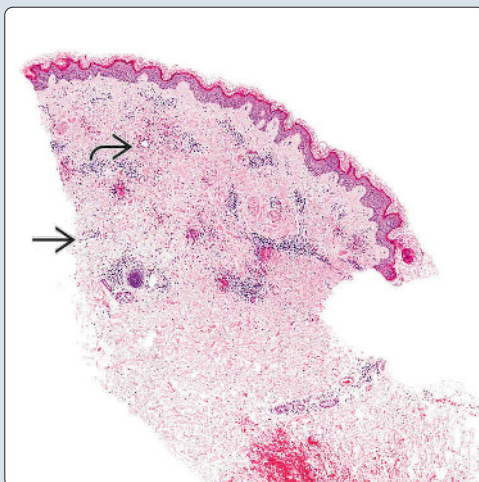
- Eosinophilic flame figures
- Interstitial infiltrate of eosinophils admixed lymphocytes, macrophages in dermis
- Spongiosis and dermal edema may result in vesicles or bullae

### TOP DIFFERENTIAL DIAGNOSES

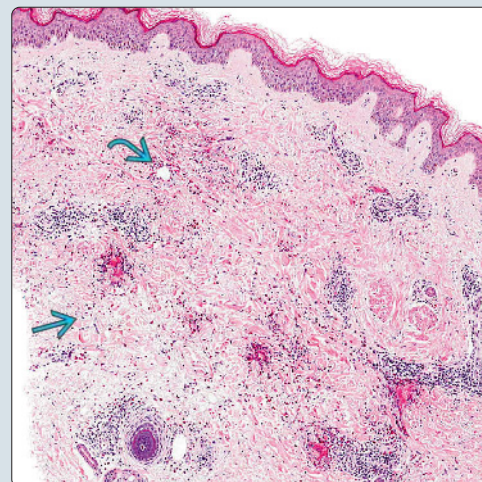
- Arthropod bite reaction
  - Look for wedge-shaped infiltrate
  - Peripheral eosinophilia is seen in most cases of Wells syndrome but not in arthropod bite reactions
- Urticarial bullous pemphigoid
  - Look for eosinophils lining up at dermal-epidermal junction
  - Direct immunofluorescence will be positive for IgG &/or C3 along dermoepidermal junction
- Dermal allergic contact dermatitis
  - Clinical correlation required
- Bacterial cellulitis or erysipelas
  - Clinically warm and tender
  - Pathology should demonstrate predominantly neutrophilic infiltrate

Perivascular and Interstitial Infiltrate

(Left) Low-power image shows a perivascular [red box] and interstitial [blue box] infiltrate of eosinophils admixed lymphocytes and macrophages in the dermis. (Right) Medium-power image shows a perivascular [red box] and interstitial [blue box] infiltrate of eosinophils, admixed lymphocytes, and macrophages in the dermis.

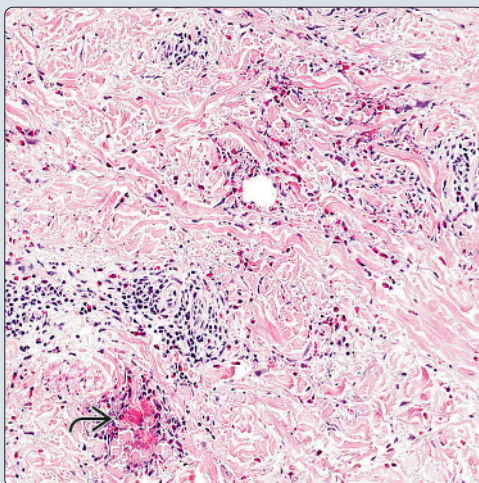


Interstitial Infiltrate

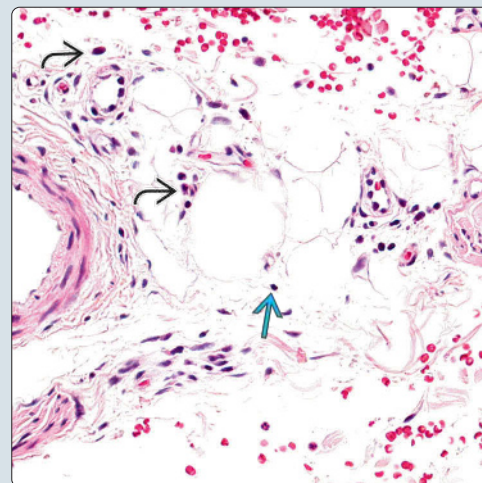


Flame Figures

(Left) Abundance of degranulating eosinophils results in flame figures [red box]. (Right) Subcutaneous fat involvement of the inflammatory infiltrate is common in eosinophilic cellulitis, and is comprised of numerous interstitial eosinophils [red box] and lymphocytes [blue box].



Extension Into Subcutaneous Fat





**TERMINOLOGY****Synonyms**

- Eosinophilic cellulitis

**ETIOLOGY/PATHOGENESIS****Pathogenesis**

- Majority of cases have no known trigger but may represent hypersensitivity to variety of agents, including insect bites/stings, myeloproliferative disease, and infection (viral, dermatophyte, parasitic)

**CLINICAL ISSUES****Epidemiology**

- Age
  - Any age, including infants, may be affected

**Presentation**

- Painful or pruritic edematous plaques or nodules
- May take on variety of morphologies, also including urticarial, annular, or bullous
  - May mimic bacterial cellulitis, Sweet syndrome, morphea, sarcoidosis
- Often symmetrical
- Lack of warmth, symmetry and occasional violaceous border suggest diagnosis

**Laboratory Tests**

- Peripheral blood eosinophilia is common

**Treatment**

- Mild cases may be treated with mid- to high-potency topical steroids with systemic therapy for more extensive disease
- Systemic therapy
  - Prednisone 10-80 mg PO daily, tapered over 1 month
  - Other reported therapies include
    - Cyclosporine 1.5-2.5 mg/kg/day
    - Minocycline
    - Hydroxychloroquine
    - Dapsone
- Oral antihistamines may be utilized to treat pruritus

**Prognosis**

- With treatment, response if often rapid
- Without treatment, lesions tend to resolve spontaneously within 4-8 weeks
- Flares or recurrences are not uncommon

**MICROSCOPIC****Histologic Features**

- Interstitial infiltrate of eosinophils admixed lymphocytes, macrophages in dermis
- Spongiosis and dermal edema may result in vesicles or bullae
- Eosinophilic flame figures
- Infiltrate often extends into subcutis with deep interstitial eosinophils that histopathologically resembles bug bite
  - Inflammatory infiltrate is often more diffuse though, and not classically wedge-shaped

**DIFFERENTIAL DIAGNOSIS****Arthropod Bite Reaction**

- Distinguish clinically as pathology may be very similar (flame figures can be present in both)
- Look for wedge-shaped infiltrate
- Peripheral eosinophilia is seen in most cases of Wells syndrome but not in arthropod bite reactions

**Urticarial Bullous Pemphigoid**

- Look for eosinophils lining up at dermal-epidermal junction
- Direct immunofluorescence will be positive for IgG &/or C3 along dermoepidermal junction

**Dermal Allergic Contact Dermatitis**

- May have nearly identical pathological features including flame figures
- Typically, infiltrate is not as deep
- Clinical correlation required

**Bacterial Cellulitis or Erysipelas**

- Clinically warm and tender
- Pathology should demonstrate predominantly neutrophilic infiltrate

**DIAGNOSTIC CHECKLIST****Clinically Relevant Pathologic Features**

- Clinical correlation is required as flame figures are hallmark, but not unique to this disease

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## KEY FACTS

### TERMINOLOGY

- Cutaneous tissues destroyed by heat, electricity, radiation, or caustic chemicals

### ETIOLOGY/PATHOGENESIS

- Excessive sun exposure, fire, radiant heat, radiation, chemical, or electrical contact
- Partial-thickness burns can progress for 2-4 days after initial exposure
- Temperature and duration of exposure have synergistic effect
- Greater temperature extremes require shorter exposure times to result in cell death
- Pulmonary: Edema (related to size and depth of burn wound), impaired gas exchange

### CLINICAL ISSUES



- 1st-degree burns (superficial): Painful, dry, erythematous, nonblistered skin

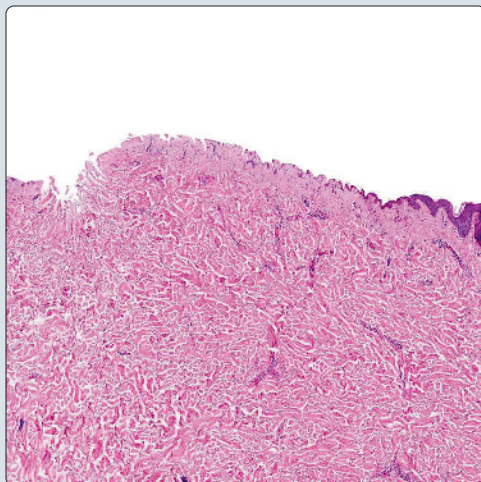
- Painful, dry, erythematous nonblistered skin
- 2nd-degree burns (partial thickness)
  - Superficial: Painful, erythematous blistering (within 24 hours)
  - Deep: Damage hair follicles and glandular tissue, can be moist or waxy and dry
- 3rd-degree burns (full thickness)
  - Varies from waxy white, leathery gray, to charred black
  - Skin is dry and inelastic, does not blanch with pressure

### MICROSCOPIC

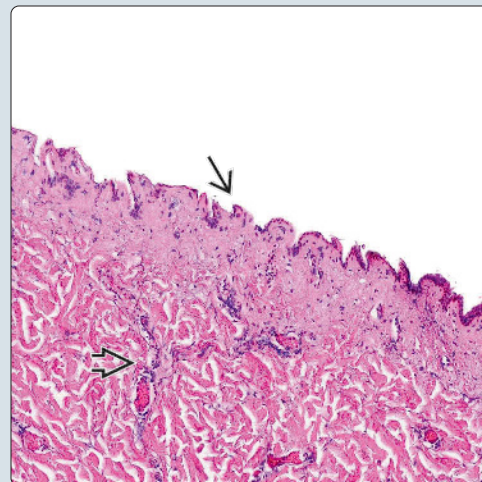
- Coagulative necrosis of epidermis (devitalized tissue)
- Vital tissue reaction
- Influx of acute followed by chronic inflammatory cells
- Vascular proliferation
- Edema (due to increased vascular permeability and new vessel formation)

Loss of Epidermis







**(Left)** An acute 1st-degree burn shows loss of epidermis, minimal dermal changes, and no inflammatory infiltrate. **(Right)** Acute 1st-degree burn with loss of epidermis, preservation of underlying dermal papillae architecture , and minimal perivascular inflammatory cell infiltrate  is shown.

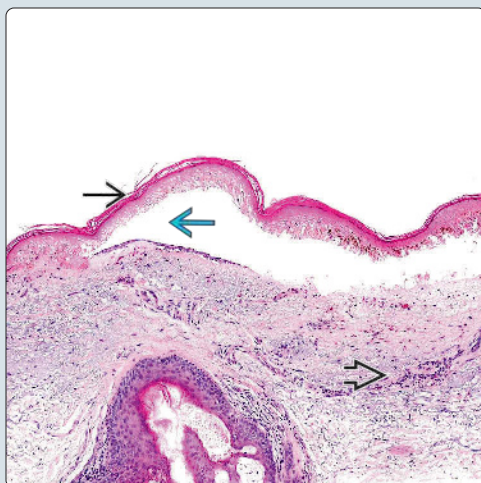


Loss of Epidermis With Preservation of Dermal Papillae

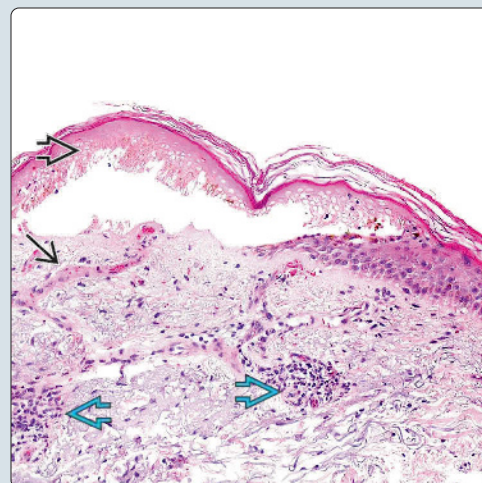


Full-Thickness Epidermal Necrosis

**(Left)** Biopsy of a burn shows full-thickness epidermal necrosis  with separation from the dermis . Scant mixed inflammatory cell infiltrate is in the dermis . **(Right)** The edge of a 1st-degree burn shows full-thickness epidermal necrosis , endothelial swelling , and perivascular mixed inflammatory cell infiltrate .



Epidermis Necrosis and Endothelial Swelling





## TERMINOLOGY

### Synonyms

- Thermal burn
- Burn injury

### Definitions

- Traumatic injury caused by thermal exposures
- Cutaneous tissues destroyed by heat, electricity, radiation, or caustic chemicals

## ETIOLOGY/PATHOGENESIS

### Environmental Exposure

- Excessive sun exposure
- Fire
- Radiant heat
- Radiation
- Chemical contact
- Electrical contact

### Iatrogenic Causes

- Laser therapies
- Cauterization

### Progression

- Partial-thickness burns can progress for 2-4 days after initial exposure

### Cellular Responses to Thermal Excess

- Protein denaturation
- Loss of cellular membrane integrity
- Cumulating in cell death (apoptosis or necrosis)
- Temperature and duration of exposure have synergistic effect
  - Greater temperature extremes require shorter exposure times to result in cell death

### Burn Shock Pathophysiology

- Toxic metabolites and immunomodulators are released locally with cell destruction
  - Histamine
  - Serotonin
  - Bradykinin
  - Nitric oxide
  - Oxygen-free radicals
  - Prostaglandins
  - Thromboxanes
  - Tumor necrosis factor
  - Interleukins
- Early increased microvascular permeability
  - Histamine mediated
- Local edema
  - Mediated by histamine, oxygen-free radicals
- Influx of inflammatory mediators
  - VEGF
  - PDGF
  - TGF- $\beta$
  - Regulate wound healing and scar formation

### Burn Zonation

- Zone of hyperemia

- Vasodilation and inflammation, no damage
- Zone of stasis
  - Variable prognosis of tissues in this zone with potential to heal or devitalize and progress
  - Vascular stasis and ischemia
  - Revascularization within few days can salvage tissue
    - Ischemia-reperfusion injury risk
- Zone of coagulation
  - Necrotic tissue, bears brunt of thermal tissue damage

### Systemic Effects

- Extreme hypermetabolism/catabolism
  - Heat and fluid loss from burn wounds
- Shock
- Multiorgan failure
  - Cardiovascular
    - Hypovolemia due to fluid loss from wounds
    - Edema and hypoproteinemia
    - Myocardial depression
  - Gastrointestinal
    - Impaired motility and absorption
    - Vasoconstriction
    - Decreased mucosal integrity
    - Bacterial transmigration
  - Hematopoietic
    - Immunosuppression
  - Renal
    - Hypovolemia
    - Vasoconstriction
    - Acute tubular necrosis
  - Pulmonary
    - Edema (related to size and depth of burn wound)
    - Impaired gas exchange
    - Smoke inhalation and direct thermal injury to lungs commonly accompany thermal injury

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - 1.2 million people per year in USA with 60,000 hospitalizations and 6,000 deaths
- Sex
  - Flame-related burns and scalding are more common in women and children
  - Electrical and chemical burns more common in men
- Risk factors
  - Low socioeconomic status
  - Younger age
  - Loose, flammable clothing and use of flammable liquids

### Presentation

- 1st-degree burns (superficial)
  - Painful, dry, erythematous, nonblistered skin
  - Usually from sun exposure
- 2nd-degree burns (partial thickness)
  - May be superficial or deep
  - Superficial: Painful, erythematous blistering (within 24 hours)
  - Deep: Damage hair follicles and glandular tissue, can be moist or waxy and dry

- 3rd-degree burns (full thickness)
  - Varies from waxy white, leathery gray, to charred black
  - Skin is dry and inelastic, does not blanch with pressure
  - No blisters or vesicles develop
  - Lesions may extend into subcutaneous tissue, muscles, and bones
  - Less painful (nerves are destroyed)

## Treatment

- Surgical approaches
  - For deep partial-thickness (2nd-degree) and full-thickness (3rd-degree) burns
  - Early excision of devitalized tissue of deep partial- and full-thickness burns
    - Reduces burn shock pathophysiology and systemic effects
  - Skin grafts
    - Split- or full-thickness autologous
    - Allogenic
  - Fat injection (lipofilling) can improve function and aesthetics of scars
- 1st-degree burns do not require hospitalization
  - Cooling with water (room temp or cooled) can halt injury progression, aid epithelialization, and reduce scarring
- 2nd- and 3rd-degree burns usually require hospitalization
  - Supportive care
    - Fluid resuscitation and airway protection are important emergent therapies
    - Temperature regulation and infection prevention/control

## Prognosis

- Older age is associated with more comorbidities, complications, and prolonged healing times
- Variable prognosis, depending on depth of burn, surface area involved, and systemic effects
  - Increased surface area involved correlates to greater morbidity and mortality
    - 20-25% total body surface area (TBSA)
      - Requires IV fluid resuscitation
    - 30-40% TBSA likely fatal without treatment
  - Systemic effects portend worse prognosis
    - Loss of thermoregulation
    - Dehydration due to increased evaporative losses
    - Pulmonary alveolar injury (from inhalation of heated gases)
- 1st-degree burns
  - Spontaneous epidermal regeneration (2nd intention healing) within 5-7 days
  - Good prognosis
- 2nd-degree burns
  - Prognosis dependent on depth and extent of burn (percentage body surface area)
  - Superficial
    - Heals by secondary intention within 14-21 days, leaving minimal scar tissue
  - Deep
    - Heals with secondary intention over 3+ weeks with scar tissue formation and decreased mobility and function
- 3rd-degree burns

- Prognosis dependent on depth and extent of burn (percentage body surface area)
- Heals by contraction of edges of wound and scar tissue deposition
- Fragile repair is susceptible to breakdown and protracted healing
- Wound infection is common

## MACROSCOPIC

### General Features

- 1st-degree burn
  - Dry red, painful
  - Blisters are uncommon
  - Similar to sunburn
- 2nd-degree burns
  - Varying from moist wet to waxy dry with mottled colorization
  - Often with blister formation
  - Varied color from red with blanching to cheesy white that does not blanch with pressure
  - Extremely painful (with decreasing pain in deeper burns)
- 3rd-degree burns
  - Vary from waxy white, leathery gray, to charred black
  - Skin is dry and inelastic and does not blanch with pressure
  - No blisters or vesicles develop
  - Lesions may extend into subcutaneous tissue, muscles, and bones

## MICROSCOPIC

### Histologic Features

- Coagulative necrosis of epidermis (devitalized tissue)
  - Variable extension into dermis (2nd-degree burns) or subcutaneous tissues (3rd-degree burns)
- Vital tissue reaction
  - Influx of acute followed by chronic inflammatory cells
  - Vascular proliferation
  - Edema (due to increased vascular permeability and new vessel formation)
  - Deposition of collagen (scar formation) by fibroblasts
- Burns extending to or through subcutis (3rd-degree burns)
  - Vascular proliferation and collagen deposition by fibroblasts can be found in dermal tissues immediately adjacent to burn

## ANCILLARY TESTS

### Culture of Tissue as Necessary

- Wound infection by opportunistic agents (bacterial and fungal) are common in wounds with protracted healing

## DIFFERENTIAL DIAGNOSIS

### Artifact of Tissues Resected Using Electrocautery or Artifact of Poor Fixation

- Artifacts will not show vital tissue reaction

### Erythema Multiforme

- Acute epidermal necrosis without devitalization of corneal layer
- Targetoid lesions clinically



- Can differentiate with clinical impression and histology

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Depth and extent of thermal injury dictate prognosis
- Partial-thickness burns can progress for 2-4 days after initial exposure
- Treatment includes
  - Early excision of devitalized tissue of deep partial- and full-thickness burns
  - Skin grafts for large 2nd-degree and most 3rd-degree burns
  - Supportive care to maintain hydration and internal temperature control (due to increased evaporative losses)

### Pathologic Interpretation Pearls

- Must differentiate from erythema multiforme (epidermal necrosis with unaffected corneal layer)
- Cultures (blood and tissue) may need to be repeated to monitor for secondary infection

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## KEY FACTS

### TERMINOLOGY

- Synonyms include talon noir

### ETIOLOGY/PATHOGENESIS

- Mechanical traumatization of vessels in papillary dermis

### CLINICAL ISSUES

- Often mistaken for acral melanoma, clinically
- Classic lesion is described as linear or grouped pigmented, dark brown-black macules on heel
  - However, well-demarcated pigmented patches on palms or soles, brown macules on pressure points, such as ball of foot, or blackish macules on dorsal and distal tips of toes have all been described
- Paring stratum corneum with blade is painless procedure that will remove pigment in black heel (BH)

### MICROSCOPIC

- Intracorneal hemorrhage

### ANCILLARY TESTS

- Benzidine stain is positive, while iron stains are negative
- Dermoscopy demonstrates grouped globular or punctate hemorrhages with homogeneous red-black color, often in linear pattern and with satellite globules

### TOP DIFFERENTIAL DIAGNOSES


- Acral nevus
- Acral melanoma
- Ecchymosis
- Tinea nigra
- Viral warts

### DIAGNOSTIC CHECKLIST

- Intracorneal hematoma or coagulated blood may be seen

Intracorneal Hemorrhage and Pigmented Macule on Great Toe



Black heel (talon noir) on biopsy shows an intracorneal hemorrhage  on acral skin. This shave biopsy was performed to exclude melanoma. Talon noir clinically (inset) presents as a pigmented macule on the great toe simulating an acral nevus. (Courtesy S. Hsu, MD.)



**TERMINOLOGY****Abbreviations**

- Black heel (BH)

**Synonyms**

- Talon noir
- Calcaneal petechiae
- Intracorneal hemorrhage
- Basketball or tennis heel

**Definitions**

- Intracorneal hemorrhage on acral skin due to local trauma

**ETIOLOGY/PATHOGENESIS****Trauma**

- Following trauma to minimally protected vessels in papillary dermis, transepidermal elimination results in intracorneal hematoma
- Causative trauma includes lateral shearing forces
  - Can also result from applied pressure, friction, or thermal injury

**CLINICAL ISSUES****Presentation**

- Classic lesion is described as linear or grouped pigmented, dark brown-black macules on heel
  - However, well-demarcated pigmented patches on palms or soles, brown macules on pressure points, such as ball of foot, or blackish macules on dorsal and distal tips of toes have all been described
- Noninvasive measures can be undertaken to avoid skin biopsy when diagnosis of BH is considered
  - Paring stratum corneum with blade is painless procedure that will remove pigment in BH
    - In contrast, this procedure will not eliminate epidermal &/or dermal pigment of melanocytic neoplasm
  - Dermoscopy is another helpful adjunct study

**Treatment**

- No treatment is required given that BH is benign and self-limited

**MICROSCOPIC****Histologic Features**

- Hyperkeratosis with lakes of intra- or subcorneal hemorrhage are present
  - Coagulated blood, seen as eosinophilic amorphous material, may also be seen in stratum corneum
- Although intracorneal blood deposits are inaccessible to degradative action of macrophages, extravasated erythrocytes and siderophages may be found in papillary dermis

**ANCILLARY TESTS****Histochemistry**

- Benzidine stain is specific for detection of hemoglobin and can be used to highlight intracorneal blood if necessary

- Iron stains, such as Prussian blue, will not stain intracorneal deposits and are only positive if dermal hemorrhage is present

**Dermoscopy**

- Demonstrates grouped globular or punctate hemorrhages with homogeneous red-black color, often in linear pattern and with satellite globules
  - In contrast, acral melanoma demonstrates accentuation on dermatoglyphic ridges with variable color, while acral nevi accentuate furrows

**DIFFERENTIAL DIAGNOSIS****Acral Nevus and Melanoma**

- Should only cause clinical confusion
- Superficially sampled acral melanocytic lesions subjected to trauma may show similar histopathologic findings
  - Deeper biopsies are easy to distinguish

**Purpura or Ecchymosis**

- Dermal hemorrhage instead of intracorneal

**Tinea Nigra**

- Dematiaceous hyphae in stratum corneum

**Viral Warts**

- Microscopy demonstrates verrucous parakeratosis, papillomatosis, and sometimes koilocytes
- Dermoscopy highlights thrombosed capillaries within verrucous lobules

**DIAGNOSTIC CHECKLIST****Clinically Relevant Pathologic Features**

- Hemorrhage within or beneath stratum corneum

**Pathologic Interpretation Pearls**

- Instead of hemorrhage, may only see coagulated blood as amorphous pink deposits

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## KEY FACTS

### CLINICAL ISSUES

- Presentation
  - One or multiple papule(s), may be pedunculated
  - Usually present in neonates
  - Presentation in later childhood or adulthood is common
    - Due primarily to cosmetic concern
  - Commonly anterior to tragus in preauricular skin
    - May appear anywhere on migration path of 1st branchial arch
  - May occur individually or as part of genetic syndrome
- Associated genetic syndromes
  - Goldenhar syndrome (oculo-auriculo-vertebral syndrome)
  - Townes-Brocks syndrome
  - Treacher Collins syndrome (mandibulofacial dysostosis)
  - VACTERL syndrome
  - Wolf-Hirschhorn syndrome
- Incidence

- Present in approximately 3-6 per 1,000 live births

### MICROSCOPIC

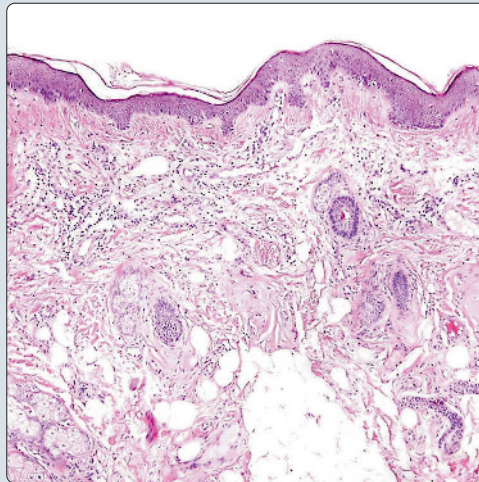
- Overlying epidermis may have rugated appearance
- Dermis contains numerous vellus hair follicles
- Cartilage is present at center of specimen in nearly all cases
- Some cases may have central fibroadipose tissue
- Prominent fibrous framework within adipose tissue
- Sebaceous glands are small and not well developed

### TOP DIFFERENTIAL DIAGNOSES

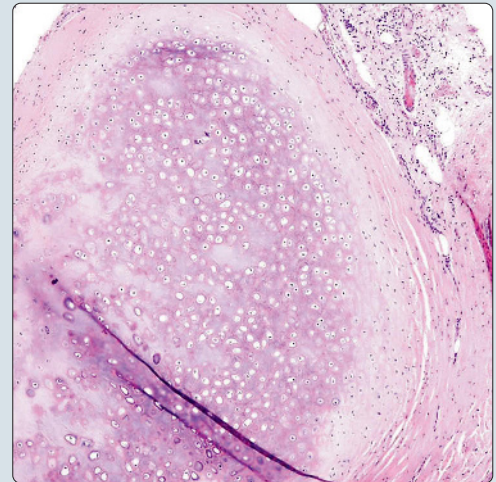
- Skin tag (acrochordon)
- Intradermal nevus
- Hair follicle nevus
- Bronchogenic cyst
- Choristoma
- Chondroid syringoma (mixed tumor)

Overlying Skin of Accessory Tragus

**(Left)** The epidermis is usually unremarkable without acanthosis or significant hyperkeratosis. Sparse inflammatory cells are present and there is a mild proliferation of small hair follicles. **(Right)** In an ideal biopsy, the center of the accessory tragus includes a core of mature cartilage.

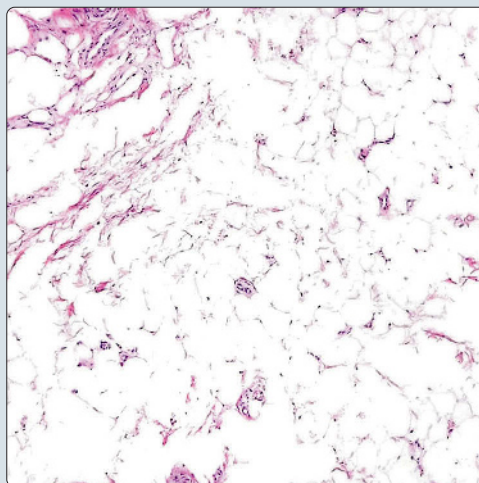


Cartilaginous Core

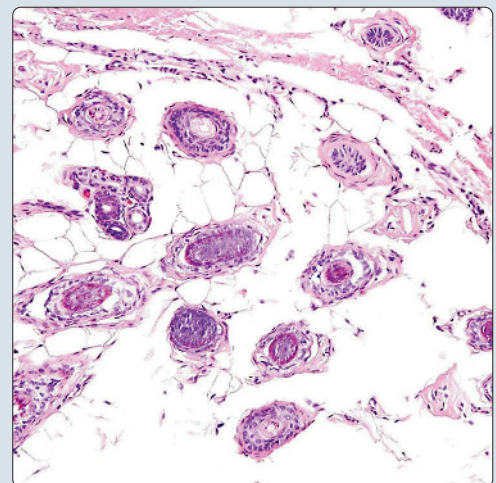


Adipose Tissue Core

**(Left)** In some cases, a cartilaginous core is not seen. Instead, the center may consist of adipose tissue, potentially causing confusion with lipoma or acrochordon. **(Right)** The center of some accessory tragi have a small hair follicle proliferation admixed with adipose tissue.



Hair Follicle Proliferation





**CLINICAL ISSUES****Presentation**

- One or multiple papule(s), may be pedunculated
  - Usually present in neonates
  - Presentation in later childhood or adulthood is common
    - Due primarily to cosmetic concern
- Commonly anterior to tragus in preauricular skin
  - May appear anywhere on migration path of 1st branchial arch
    - Angle of mouth to ear, also may be present on neck or anterior to sternocleidomastoid muscle
- No pain, pruritus, or distinct coloration
- May occur individually or as part of genetic syndrome

**Treatment**

- Excision is curative

**Prognosis**

- Not locally aggressive and does not recur after removal
- Shave biopsy through cartilage core may lead to poor or incomplete wound healing

**Disease Associations**

- Goldenhar syndrome (oculo-auriculo-vertebral syndrome)
  - Accessory tragus: Constant feature in this syndrome
  - Epibulbar desmoids
  - Vertebral defects
- Treacher Collins syndrome (mandibulofacial dysostosis)
  - Malformed or absent ears, ± accessory tragus
  - Conductive hearing loss
  - Downward-slanting eyes
  - Micrognathia
  - Underdeveloped zygoma
  - Drooping of lower lateral eyelids
- Townes-Brocks syndrome
  - External ear abnormalities, including possible accessory tragus
  - Anorectal malformations
  - Renal, heart, and hand-foot abnormalities
- VACTERL syndrome
  - Vertebral anomalies, anal atresia, cardiac defects, tracheoesophageal fistula, esophageal atresia, renal and radial abnormalities, limb defects
- Wolf-Hirschhorn syndrome
  - Microcephaly, micrognathia, short philtrum, prominent glabella, ocular hypertelorism, dysplastic ears, and preauricular tags (may be accessory tragus)
  - Growth restriction
  - Learning difficulties or intellectual disability
  - Muscle hypotonia
  - Seizures
  - Heart defects

**Incidence**

- Present in approximately 3-6 per 1,000 live births

**MICROSCOPIC****Histologic Features**

- Overlying epidermis may have rugated appearance

- Stratum corneum is usually normal thickness but may be thinned
- Dermis contains numerous vellus hair follicles
- Dilated blood vessels are present in papillary dermis
- Cartilage is present at center of specimen in nearly all cases
  - Some cases may have central fibroadipose tissue
    - Prominent fibrous framework within adipose tissue
- Sebaceous glands are small and not well developed
- Eccrine glands are typically present
- Nerves are present and may be enlarged

**DIFFERENTIAL DIAGNOSIS****Clinical**

- Skin tag (acrochordon)
  - Papule or pedunculated
  - More wrinkled, rugated surface
- Intradermal nevus
  - Smooth surface
  - ± pigmentation

**Histopathological**

- Skin tag (acrochordon)
  - No proliferation of vellus hairs
  - No cartilage center
- Hair follicle nevus
  - Composed exclusively of vellus hairs
  - No cartilage center
  - Should not have adipose tissue like that seen in accessory tragus
- Bronchogenic cyst
  - Cyst usually lined by respiratory epithelium
  - Foci of cartilage around cyst
  - May have ectopic gastric mucosa as well
- Choristoma
  - Definition: Excess of tissue in an abnormal location (heterotopic tissue)
  - Cartilage may be present, other tissue types present as well
  - Rare in skin
- Chondroid syringoma (mixed tumor)
  - Proliferation of eccrine sweat duct epithelium (may have somewhat basaloid appearance)
  - Myoepithelial cells present
  - Myxoid or cartilaginous areas
  - Virtually identical to salivary gland pleomorphic adenomas (mixed tumors)

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## KEY FACTS

### ETIOLOGY/PATHOGENESIS

- Extramammary breast tissue (nipple, areola, and glandular breast tissue) may arise from anywhere along mammary ridge (midaxilla to inguinal area)

### CLINICAL ISSUES

- Benign condition
- Can have same spectrum of diseases as normal breast tissue
- Some cases are associated with increased risk of renal adenocarcinoma, testicular cancer, prostate cancer, and urinary bladder carcinoma
- Simple excision is treatment of choice if lesion is irritated or of cosmetic concern

### MACROSCOPIC

- Well-demarcated, slightly hyperpigmented or skin-colored papule, with typical central elevation and surrounding areola

### MICROSCOPIC

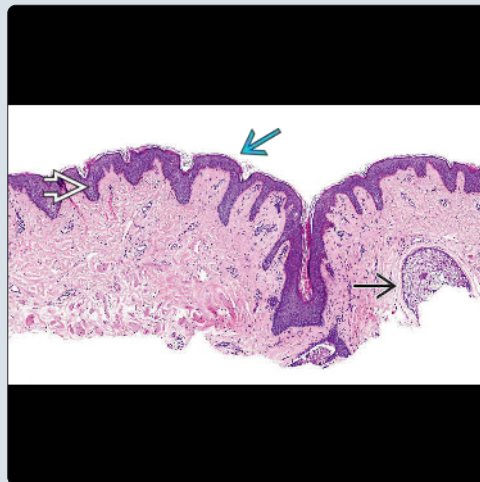
- Epidermal papillomatosis and acanthosis with minimal hyperkeratosis
- Basal cell layer hyperpigmentation
- Increased dermal pilosebaceous follicles and smooth muscle bundles

### TOP DIFFERENTIAL DIAGNOSES

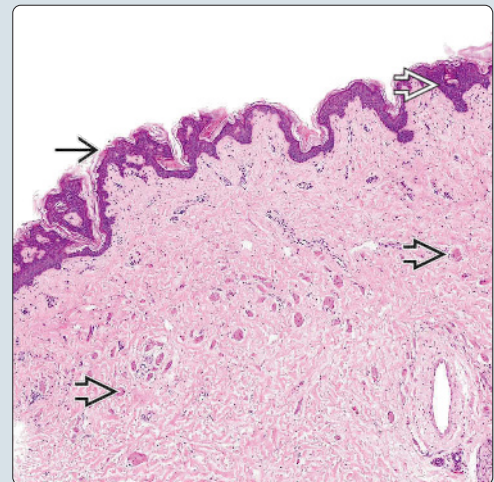
- Lentigo
- Melanocytic nevus
- Melanoma
- Dermatofibroma
- Lipoma
- Becker nevus

#### Acanthosis and Papillomatosis With Sebaceous Lobule

(Left) Epidermal acanthosis and subtle papillomatosis with a dermal sebaceous lobule are seen in a supernumerary nipple biopsy. (Right) Accessory nipple shows papillomatosis with subtle epidermal acanthosis and increased dermal smooth muscle bundles.

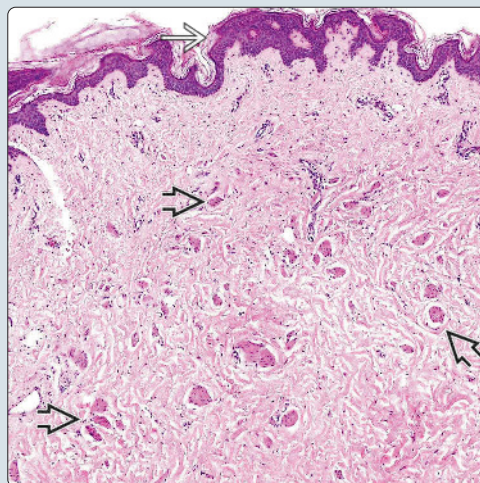


#### Increased Dermal Smooth Muscle Bundles

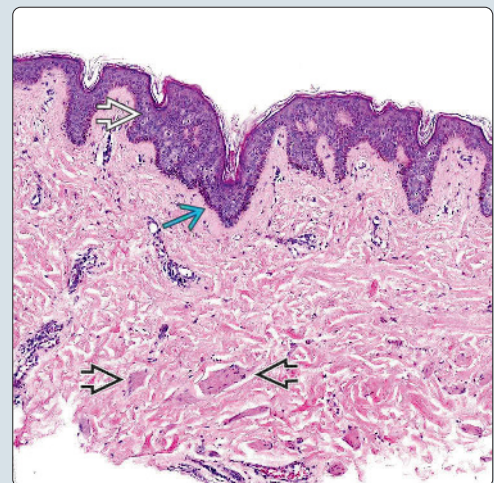


#### Papillomatosis With Increased Smooth Muscle Bundles

(Left) Supernumerary nipple biopsy shows epidermal papillomatosis, some basal layer hyperpigmentation, and increased dermal smooth muscle bundles. (Right) Accessory nipple shows acanthosis with subtle basal cell hyperpigmentation and increased dermal smooth muscle bundles.



#### Acanthosis, Basal Layer Hyperpigmentation, and Smooth Muscle Bundles





## TERMINOLOGY

### Abbreviations

- Supernumerary nipple (SNN)

### Synonyms

- Accessory nipple

### Definitions

- Congenital accessory breast tissue without glandular structures
- Polythelia: Accessory nipple (no glandular breast tissue or areola)
- Polythelia areolaris: Accessory areola (no nipple or glandular breast tissue)
- Polymastia: Accessory breast including nipple, areola, and glandular breast tissue

## ETIOLOGY/PATHOGENESIS

### Developmental Anomaly

- During embryogenesis, nipples arise from pair of mammary ridges extending along ventral body wall
  - Extramammary glands may also arise from anywhere along mammary ridge (midaxilla to inguinal area)
  - Failure of these structures to regress results in SNN
- Association with renal or urogenital anomalies suggested by some studies, whereas other studies have failed to show this association

### Usually Sporadic but Can Be Familial

- Typically autosomal dominant with variable penetrance
- Can also be X-linked dominant

### 8 Classifications of Supernumerary Breast Tissue (Kajava Categories)

- Complete breast with nipple, areola, and gland tissue (polymastia)
- Gland tissue and nipple without areola
- Areola and gland tissue without nipple
- Gland tissue only
- Nipple and areola with replacement of gland tissue by fat (pseudomamma)
- Nipple only (polythelia)
  - Most common variant
- Areola only (polythelia areolaris)
- Patch of hair only (polythelia pilosa)

## CLINICAL ISSUES

### Presentation

- Unilateral or bilateral
- May include areola, nipple, or both
- Most commonly located just inferior to normal breast
- Less frequently occur in axilla
- Extremely rare locations include thigh, vulva, sole of foot, face, midback, neck, and shoulder
- 5.6% of children exhibit 1 or more SNN

### Treatment

- Surgical approaches
  - Simple excision is treatment of choice if lesion is irritated or of cosmetic concern

### Prognosis

- Benign condition

## MACROSCOPIC

### General Features

- Well-demarcated, slightly hyperpigmented or skin-colored papule, with typical central elevation and surrounding areola

## MICROSCOPIC

### Histologic Features

- Epidermal papillomatosis and acanthosis with minimal hyperkeratosis
- Basal cell layer hyperpigmentation
- Increased dermal pilosebaceous follicles and smooth muscle bundles
- May have underlying normal breast glandular tissues

## DIFFERENTIAL DIAGNOSIS

### Lentigo

- No dermal smooth muscle proliferation
- No papillomatosis or acanthosis

### Melanocytic Nevus

- Symmetric dermal or combined junctional/dermal proliferation of benign melanocytes

### Melanoma

- Asymmetric junctional &/or dermal proliferation of atypical melanocytes with mitosis (may be atypical) and overlying epidermal pagetoid spread

### Dermatofibroma

- Dermal proliferation of bland spindled cells in short, interlacing fascicles with peripheral infiltration around individual collagen bundles

### Lipoma

- Well-circumscribed dermal to subcutaneous collection of benign lipocytes

### Becker Nevus

- Epidermal acanthosis with increased basal cell layer pigmentation due to benign melanocyte hyperplasia
- Smooth muscle hamartoma: Increased irregular dermal smooth muscle bundles that are not associated with hair follicles or sebaceous glands
- Variable hypertrichosis (increased terminal hair follicles)

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